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Proposed Registration Decision PRD2016-22

Imidacloprid

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Overview

Proposed Registration Decision for Imidacloprid

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Bay NTN 33893 Technical Insecticide and its end-use products, Temprid SC Insecticide and Temprid ReadySpray Insecticide, containing the technical grade active ingredient imidacloprid. The end-use products are coformulated with beta-cyfluthrin to kill several arthropod pests including bed bugs.

BAY NTN 33893 Technical Insecticide (Registration Number 24468 is currently registered in Canada in a variety of products for different uses including agriculture, turf grass, pet products, ant baits, cockroach baits and tree injection. The use of imidacloprid on sites such as mattresses is a new use for this active ingredient.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Bay NTN 33893 Technical, Temprid SC Insecticide and Temprid ReadySpray Insecticide.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides.

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1 *"Acceptable risks" as defined by subsection 2(2) of the Pest Control Products Act.*

2 *"Value" as defined by subsection 2(1) of the Pest Control Products Act: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact."*

For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of the Health Canada website at healthcanada.gc.ca/pmra.

Before making a final registration decision on imidacloprid, the PMRA will consider all comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on imidacloprid, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Imidacloprid?

Imidacloprid is an insecticide used to kill bed bugs. It is registered for a variety of uses, including ant baits and cockroach baits in structures. Sites such as mattresses are a new use for this insecticide. It is combined with another insecticide, beta-cyfluthrin, in two commercial class products, Temprid SC Insecticide and Temprid ReadySpray.

Health Considerations

Can Approved Uses of Imidacloprid Affect Human Health?

Products containing imidacloprid are unlikely to affect your health when used according to label directions.

Potential exposure to imidacloprid may occur through the diet (food and water) or when handling and applying end-use products containing imidacloprid. When assessing health risks, two key factors are considered: the levels at which no health effects occur in animal testing and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only those uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide-containing products are used according to label directions.

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3 *"Consultation statement" as required by subsection 28(2) of the Pest Control Products Act.*

4 *"Decision statement" as required by subsection 28(5) of the Pest Control Products Act.*

In laboratory animals, the technical grade active ingredient imidacloprid was highly acutely toxic via the oral route. It was of low acute toxicity by the dermal and inhalation routes, was minimally irritating to the eyes and non-irritating to the skin. Imidacloprid did not cause an allergic skin reaction.

The end-use product, Temprid SC Insecticide, was of slight acute toxicity via the oral route of exposure, and was of low acute toxicity via the dermal and inhalation routes. It was minimally irritating to the eyes, slightly irritating to the skin, and did not cause an allergic skin reaction.

Temprid ReadySpray Insecticide was of low acute toxicity via the oral and dermal routes of exposure and non-irritating to the eyes. It was considered to be of low acute toxicity by the inhalation route, slightly irritating to the skin and not likely to cause an allergic skin reaction.

Registrant-supplied short, and long term (lifetime) animal toxicity tests, as well as information from the published scientific literature were assessed for the potential of imidacloprid to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints for risk assessment included effects on the liver, thyroid gland and nervous system. There was no indication that the young were more sensitive than the adult animal. The risk assessment protects against the effects noted above and any other potential effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Risks in Residential and Other Non-Occupational Environments

Estimated risks from residential exposure are not of concern provided that directions specified on the label are followed.

The exposure assessments conducted for adults, youth and children when contacting mattresses treated with Temprid SC Insecticide or for adults and youth when contacting mattresses treated Temprid ReadySpray Insecticide did not identify risks of concern when used according to label directions.

Occupational Risks From Handling Imidacloprid

Occupational risks are not of concern when imidacloprid is used according to the proposed label directions, which include protective measures.

Pest Control Operators mixing, loading and applying Temprid SC Insecticide or applying Temprid ReadySpray Insecticide can come in direct contact with imidacloprid on the skin or through inhalation. Therefore, the label will specify that anyone mixing, loading and/or applying imidacloprid must wear long-sleeves, long pants, chemical-resistant gloves, and shoes plus socks.

Value Considerations

What Is the Value of Temprid SC Insecticide and Temprid ReadySpray?

Bed bugs are difficult-to-control insects that have substantial impacts on the well-being of people. Temprid SC Insecticide and Temprid ReadySpray combine two insecticides, a pyrethroid and neonicotinoid, to kill all life stages of bed bugs in sites such as mattresses.

Temprid SC Insecticide and Temprid ReadySpray kill all life stages of bed bugs on contact. The submitted value information demonstrated that combining beta-cyfluthrin and imidacloprid improves efficacy against pyrethroid-resistant bed bugs. These products may be used as part of a pest management program to kill bed bugs.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label Temprid SC Insecticide or applying Temprid ReadySpray Insecticide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

To reduce direct contact with imidacloprid on the skin, mattresses must be dry before clean linens are placed on treated mattresses.

For Pest Control Operators mixing, loading and applying Temprid SC Insecticide or applying Temprid ReadySpray Insecticide to mattresses, long-sleeves, long pants, chemical-resistant gloves, shoes and socks must be worn.

Next Steps

Before making a final registration decision on imidacloprid, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

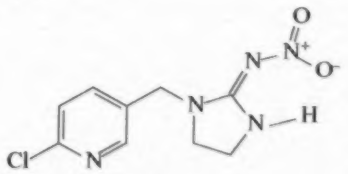
When the PMRA makes its registration decision, it will publish a Registration Decision on imidacloprid (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Imidacloprid

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Imidacloprid
Function	Insecticide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	(*E*)-1-(6-chloro-3-pyridylmethyl)-*N*-nitroimidazolidin-2-ylideneamine
2. Chemical Abstracts Service (CAS)	(2*E*)-1-[(6-chloro-3-pyridinyl)methyl]-*N*-nitro-2-imidazolidinimine
CAS number	138261-41-3
Molecular formula	$C_9H_{10}ClN_5O_2$
Molecular weight	255.67
Structural formula	
Purity of the active ingredient	98% nominal

1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product

Technical Product—BAY NTN 33893 Technical Insecticide

Property	Result
Colour and physical state	Light yellow solid
Odour	Characteristic odour, weak
Melting point	144°C
Boiling point or range	N/A
Density	1.54 g/cm^3
Vapour pressure at 20°C	4×10^{-7} mPa at 20°C 9×10^{-7} mPa at 25°C
Henry's law constant at 20°C	Relatively non-volatile under field conditions

Property	Result
Ultraviolet (UV)-visible spectrum	pH / λ_{max} (nm) 4 270 7 270 9 270
Solubility in water at 20°C	510 mg/L
Solubility in organic solvents at 20°C (g/100 mL)	Solvent / Solubility (g/L) dichloromethane 67 isopropanol 2.3 toluene 0.69 n-hexane <0.1
n-Octanol-water partition coefficient (K_{OW})	log K_{ow} = 0.57 at 21°C
Dissociation constant (pK_a)	The test substance shows very weak basic properties. Complete protonation can be achieved only in non-aqueous solvents in presence of very strong acids. It is not possible to specify a pK_a value of the test substance in pure aqueous systems.
Stability (temperature, metal)	No exothermic decomposition occurred below 150°C. The absence of any evolution of heat or gas and lack of colour change after 24 hours showed the product to be inert toward reduction by zinc and oxidation by NaOCl.

End-Use Product—Temprid SC Insecticide and Temprid ReadySpray Insecticide

Property	Temprid SC Insecticide	Temprid ReadySpray Insecticide
Colour	Opaque beige	Colourless
Odour	Chalky odour	Slight saponaceous odour
Physical state	Liquid	Liquid
Formulation type	Suspension concentrate	Pressurized product
Guarantee	Beta-cylfluthrin.....10.5% Imidacloprid.....21.0%	Beta-cylfluthrin.....0.05% Imidacloprid.....0.025%
Container material and description	Plastic jug/bottle, 240 mL - bulk	Bag-on-valve – a laminated plastic/foil pouch
Density	1.16 g/mL	1 g/mL
pH of 1% dispersion in water	6.92 at 20°C	5.7 – 6.7
Oxidizing or reducing action	Product contains no oxidizing or reducing agents.	Product contains no oxidizing or reducing agents.
Storage stability	Stable when stored at ambient temperatures for one year in commercial packaging.	Stable when stored at ambient temperatures for one year in commercial packaging.
Corrosion characteristics	Not corrosive to the packaging material	Not corrosive to the packaging material
Explodability	Not explosive	Not explosive

1.3 Directions for Use

Temprid SC Insecticide and Temprid ReadySpray Insecticide are both commercial class products that kill bed bugs in human proximal sites such as mattresses. Both products can only be applied to the tufts, seams, folds and edges on mattresses, boxsprings and upholstery. The products may also be applied to the cracks, crevices and joints on the interior frame of furniture.

Temprid SC Insecticide is formulated as a suspension concentrate with a guarantee of 21% imidacloprid and 10.5% beta-cyfluthrin. Prior to application, 1 mL of product is diluted in 1 L of water for bed bugs. The maximum application rate is 40 mL of diluted product/m^2.

Temprid ReadySpray is a ready-to-use pressurized product that has a guarantee of 0.05% imidacloprid and 0.025% beta-cyfluthrin. The maximum application rate is 40 mL product/m^2.

1.4 Mode of Action

Imidacloprid is a neonicotinoid insecticide belonging to mode of action (MOA) group 4A according to the Insecticide Resistance Action Committee's classification scheme. It kills insects, sowbugs and spiders by binding irreversibly to post-synaptic nicotinic acetylcholine receptors of the nervous system.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in BAY NTN 33893 Technical Insecticide have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The methods provided for the analysis of the two active ingredients in the formulations have been validated and assessed to be acceptable for use as enforcement analytical methods.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for imidacloprid was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. The studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The database also consisted of several studies conducted with various metabolites of imidacloprid. The database was supplemented by numerous publications from the scientific literature. Overall, the scientific quality of the data is high and the database is considered adequate to define the majority of toxic effects that may result from exposure to this pesticide.

In guideline metabolism studies in rats, methylene-^{14}C imidacloprid and imidazolidine-4,5-^{14}C imidacloprid were rapidly absorbed (peak plasma concentration 1-2.5 hours and 1-4 hours post-dosing respectively) following oral exposure, with approximately 90% of the administered dose (AD) being eliminated within 24 hours. Published in vitro data with human intestinal CaCo-2 cells demonstrated that imidacloprid crosses the transepithelial layer very quickly and completely with absorption facilitated by active transport. Urinary excretion was the major route of elimination (70-91% of the AD) in the guideline studies, with a lesser amount eliminated in feces (7-25% of the AD). Biliary excretion was an important contributor to fecal excretion as it accounted for 87% of fecal radioactivity. Only a trace amount was excreted in expired air. Total tissue burden 48 hours after dosing accounted for ≤ 1% of the AD. Tissues with the highest concentrations included liver, kidney, lung, skin and plasma with lesser amounts seen in the brain. No significant differences were noted between sexes, dose levels, or routes of administration in the guideline studies. In dogs dermally-treated with a single dose of an imidacloprid-containing formulation, peak imidacloprid residues were detected in blood at the first measured timepoint of 24 hours after application, with rapid dissipation such that residues were not detected after one week.

In addition to the parent, metabolites were identified in rat urine, including the glycine conjugate of 6-chloronicotinic acid[5], 4-hydroxy-imidacloprid[6], 5-hydroxy-imidacloprid[7], dehydro-imidacloprid[8] (olefinic metabolite), 6-chloronicotinic acid[9], the glycine conjugate of 6-S-methyl-nicotinic acid, nitroiminodehydroimidazolidine[10] and nitroiminoimidazolidine[11]. Desnitro-imidacloprid[12] was also identified in the feces. Nitrosimine-imidacloprid[13] was not detected as a biotransformation product in the standard rat metabolism study conducted with imidacloprid but was detected in the urine of rats fed a diet containing 1800 ppm of imidacloprid for one year. A metabolism study conducted with nitrosimine-imidacloprid revealed a similar pattern of absorption and excretion when compared to imidacloprid, although imidacloprid tended to accumulate in tissues to a greater extent than did the nitrosimine metabolite.

Published data demonstrate that rats given a single oral dose of imidacloprid exhibited a slightly longer time to peak concentration (12 hours) in monitored compartments than that identified in guideline studies; two metabolites (6-chloronicotinic acid and 6-hydroxynicotinic acid) also showed a peak at 12 hours. Consistent with previous findings, peak levels of imidacloprid in blood exceeded those in brain in this study; a similar pattern was observed with tissue levels of 6-chloronicotinic acid and 6-hydroxynicotinic acid. Following intraperitoneal exposure in mice,

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[5] Also known as WAK 3853.

[6] Also known as WAK 4103 or M2.

[7] Also known as M1.

[8] Also known as NTN 35884 or M6.

[9] Also known as M14.

[10] Also known as KNO 0523.

[11] Also known as NTN 33968 or KNO 0524.

[12] Also known as NTN 33823 or NTN 38014 or M9.

[13] Also known as WAK 3839 or M7.

metabolites from nitroreduction (nitrosimine-imidacloprid and desnitro-imidacloprid) and oxidative pathways were present in brain, liver and plasma. Mice deficient in aldehyde oxidase (AOX) had low levels of nitrosimine-imidacloprid and desnitro-imidacloprid in the liver, suggesting a key role for this enzyme in metabolism. In vitro data in human P450 supersomes indicated that certain CYP isoenzymes (CYP1A2, CYP2B6, CYP2D6 and CYP2E1) are also selective for the nitroreduction pathway. Significant species differences in the imidacloprid nitroreductive activity of liver cytosol were seen in vitro with levels of metabolite formation in rabbits > humans and rats > mice > dogs and cats. Human P450 supersome preparations further indicated that CYP3A4 is selective for imidazolidine oxidation.

Collectively, the metabolism data indicate two major routes of biotransformation. The first route involves hydroxylation of the imidazolidine ring by CYP3A4 to form 4-hydroxy and 5-hydroxy metabolites. These metabolites may form dihydroxy-imidacloprid, undergo glucuronidation or lose water to form the olefin metabolite. Oxidative cleavage of the 5-hydroxy metabolite yields 6-chloronicotinic acid. The second route involves nitro-reduction by either microsomal P450 enzymes or AOX to yield nitrosimine, amino-guanidine derivatives and desnitro-imidacloprid. Desnitro-imidacloprid undergoes oxidative cleavage to imidazolidine and 6-chloronicotinic acid. The 6-chloronicotinic acid from both pathways is subject to further glutathione conjugation.

Results from acute studies indicate that technical imidacloprid was highly toxic by the oral route and of low toxicity by the dermal and inhalation routes in rats. Clinical signs noted in the acute oral and inhalation studies included decreased motility, labored breathing, piloerection and transient tremors. Additional signs noted in the acute oral studies included apathy, staggering gait and spasms. Imidacloprid was minimally irritating to rabbit eyes and skin and did not show sensitizing potential in the Maximization assay in guinea pigs.

Acute oral toxicity studies on the urea and olefin metabolites of imidacloprid found them to be of slight toxicity to rats. The metabolites desnitro-imidacloprid and nitrosimine-imidacloprid were of high acute toxicity to rats; desnitro-imidacloprid was slightly more toxic than imidacloprid. Clinical signs in all of these studies were indicative of neurotoxicity.

The end-use product, Temprid SC Insecticide, was of slight acute toxicity to rats via the oral route of exposure and was of low acute toxicity via the dermal and inhalation routes. It was minimally irritating to the eyes and slightly irritating to the skin of rabbits. Temprid SC Insecticide was not a dermal sensitizer when tested in guinea pigs using the Buehler method. Temprid ReadySpray Insecticide was of low acute toxicity to rats via the oral and dermal routes of exposure. It was considered to be of low toxicity to rats via the inhalation route. It was non-irritating to the eyes of rabbits, and was considered to be slightly irritating to rabbit skin. Temprid ReadySpray was not considered to be a dermal sensitizer.

In a short-term dietary study with imidacloprid in rats, changes in clinical chemistry and histology indicative of liver injury were noted. Published short-term studies conducted with imidacloprid in rats via gavage also identified the liver as a target organ but at lower dose levels than the dietary study. Imidacloprid administration to rats and dogs caused increases in liver metabolic enzymes (mixed function oxidase and/or cytochrome P450). The effect on metabolic enzymes was not considered adverse. Administration of the metabolite nitrosimine-imidacloprid to rats via drinking water in a short-term study did not identify hepatic toxicity but instead

produced effects on white blood cells and non-specific organ weight changes; this metabolite was not considered to be more toxic than imidacloprid. Liver effects were also noted in rats in a 28-day inhalation toxicity study. A 21-day dermal toxicity study in rabbits afforded no evidence of toxicity up to the limit dose.

Effects on the kidney and eye, as well as microscopic lesions of the thyroid, were noted in the rat chronic dietary toxicity study. These microscopic lesions were described as mineralized particles in the colloid of isolated follicles and were not associated with changes in thyroid hormone levels. In the mouse dietary oncogenicity study, the main effects of imidacloprid consisted of reduced body weight, food consumption and water intake. There was no significant increase in toxicity observed with increased duration of dosing with imidacloprid. Neither the dietary carcinogenicity study in the rat nor the mouse dietary oncogenicity study provided evidence that imidacloprid was carcinogenic.

Most genotoxicity assays conducted with imidacloprid yielded negative results. Only two out of 13 registrant-conducted assays were positive and consisted of in vitro cytogenic assays conducted with human lymphocytes (clastogenicity) and Chinese hamster ovary cells (sister chromatid exchanges). No positive findings were noted in the in vivo assays. A published study showed negative results with imidacloprid in two in vitro assays in human lymphocytes (micronucleus and sister chromatid exchange assays). In the same publication, a positive result was demonstrated in an in vivo micronucleus assay in rats but only at a very high dose; negative results were noted at lower dose levels.The overall weight of evidence for imidacloprid did not suggest that it was genotoxic.

Reverse mutation assays with the urea and olefin metabolites of imidacloprid, desnitro-imidacloprid and nitrosimine-imidacloprid were negative. An additional ten genotoxicity studies (in vitro and in vivo) on nitrosimine-imidacloprid were also negative.

The dietary reproduction study in rats provided no evidence that imidacloprid was a reproductive toxicant. In that study, only reductions in body weight gains in parental animals (premating) and pups (during lactation) were noted. A published 60-day gavage study in rats noted disturbed estrous cyclicity; this study however, was conducted with formulated imidacloprid, and thus it is uncertain if these effects were attributable solely to imidacloprid. A 90-day published study in rats with imidacloprid, also by the gavage route, identified increased FSH, decreased LH and progesterone levels and decreased relative ovary weights only at the highest dose tested; this dose also produced clear signs of neurotoxicity and hepatotoxicity as well as evidence of lipid peroxidation and oxidative stress in the ovary. A battery of studies performed for the U.S. Endocrine Disruption Screening Program was negative for effects on the estrogen or androgen hormonal pathway or the steroidogenic pathway, however hormone levels were not measured directly in the in vivo studies. Overall there is a low level of concern for effects on hormones or endocrine organs as the findings only occurred at doses in the presence of other markers of toxicity.

In a rabbit gavage developmental toxicity study with imidacloprid, mortality and reduced body weight, body weight gain and food consumption were noted in dams. Increased abortions and total litter resorptions, decreased fetal weight and a slight increase in skeletal alterations were also noted at doses that caused significant maternal toxicity (that is, mortality, body weight loss).

In a rat gavage developmental toxicity study with imidacloprid, dams had decreased body weight gains while in fetuses there was a slight increase in the incidence of wavy ribs at a maternally-toxic dose. Results of the reproduction and developmental toxicity studies did not provide evidence of increased sensitivity in young.

Results of acute neurotoxicity testing showed that imidacloprid induced tremors, gait abnormalities, and righting reflex impairments as well as reductions in grip strength, response to stimuli, body temperature and motor/locomotor activity; reduced motor and locomotor activity was noted in females at the lowest dose tested. Reduced grip strength was also noted in male rats in the subchronic neurotoxicity study. Clinical signs of neurotoxicity (that is, trembling and severe tremors) were noted early in a 90-day oral dog study but were not observed at all in a 12-month oral dog study, where higher doses were used. The discrepancy between the findings in these two studies was attributed to the different type of feed in which imidacloprid was admixed prior to administration. Despite this discrepancy, the dog appeared to be the species most sensitive overall to the toxic effects of imidacloprid. Inconsistent effects on brain cholinesterase were seen in several imidacloprid studies; the significance of these alterations was not clear.

Neonicotinoid insecticides bind to nicotinic acetylcholine receptors (nAChRs) and, similar to nicotine, mimic the action of acetylcholine by opening the ion channels in the central and peripheral nervous system to allow sodium and calcium into cells. Activation of the receptors causes initial nervous stimulation but high and prolonged levels of activation can lead to blockage of the receptors. Whereas nicotine is selective for mammalian nAChR due to its ionized state, neonicotinoids are selective for insect nAChRs. Notwithstanding this generality, a number of published papers confirm that imidacloprid does affect mammalian nAChR in vitro with differences noted depending on the nAChR subtype. Imidacloprid demonstrated weak nAChR agonist activity in electrophysiological studies with mouse cochlear nucleus cells and human embryonic kidney cells stably expressing human $\alpha4\beta2$ receptors. Low affinity was seen for imidacloprid for the α_1 subtype in the electric organ of a Torpedo electric ray and for the α_3 and α_7 subtypes in human neuroblastoma cells. While the receptor studies collectively indicated weak activity for imidacloprid, desnitro-imidacloprid was shown to have more biological activity. Whereas nicotine binding with imidacloprid and its olefin metabolite was much greater in houseflies than in mouse brain membranes, desnitro-imidacloprid demonstrated selective activity in the mouse brain membrane. The high affinity and potency of desnitro-imidacloprid was confirmed in mouse fibroblast cells stably transfected with $\alpha4\beta2$ receptors; affinity and potency of this metabolite was comparable to nicotine. Desnitro-imidacloprid was shown to activate the extracellular signal-related kinase cascade via interaction with neuronal $\alpha4\beta2$ receptors in mouse neuroblast cells with a similar potency as nicotine.

In addition to normal neurological function, nAChRs play a key role in neurodevelopment. In one published study, cultured cerebellar granule cells from neonatal rats (expressing α_3, α_4 and α_7 subtypes) were exposed to low concentrations of imidacloprid. Intracellular calcium mobilization suggested agonist activity however the neurons were likely fully differentiated at the time of the measures due to the prolonged duration of cell culture. Accordingly, the result is more relevant to adult neurotoxicity than developmental neurotoxicity. In another paper, offspring from rats exposed to a high dose of imidacloprid on a single day of gestation via the intraperitoneal route demonstrated decreased sensorimotor performance. Increased ligand binding for the muscarinic acetylcholine receptor (m2mAChR) was observed in these offspring but no effect was apparent

on $\alpha 4\beta 2$ nAChR. In a registrant-conducted developmental neurotoxicity study, decreases in locomotor activity and in the thickness of caudate/putamen as well as impaired learning on one trial in the water maze test were noted in offspring at the highest dose level tested. This dose level produced effects on body weight and food consumption in the maternal animals. A NOAEL for the reduced caudate/putamen width was not established as morphometric assessments were not performed on offspring from the low and mid dose groups. The level of concern for the missing information was low since there was no indication of adverse functional changes in the young at the low and mid dose levels and the magnitude of the change in the caudate/putamen width was small (2-5%). As previously noted, this effect occurred at a dose level that was toxic to maternal animals.

Additional effects noted with imidacloprid in published papers included lipid peroxidation in liver and kidney tissue and evidence of oxidative stress in rat liver and brain tissue following repeated oral exposure. Increased lipid peroxidation and markers of oxidative stress were also seen with acute oral and intravenous exposure to imidacloprid in rats. Inflammatory changes in brain and liver were seen following acute intravenous imidacloprid exposure in rats.

Case reports of intentional exposures (suicides) to imidacloprid indicate that symptoms in humans consist of nausea, vomiting, headache, dizziness, abdominal pain and diarrhea. In one published paper, 28 patients with symptoms had plasma concentrations ranging from 0.02 to 51 ng/L (median 10.6 ng/L); recovery was seen in the 56 patients reported in this paper. Several case reports were available in which the patients died of cardiac complications following imidacloprid ingestion; in some of these cases, pre-existing cardiovascular disease may have been a contributing factor. In contrast to observations in some of the animal toxicity studies, cholinesterase activity was normal in these patients.

Changes were made to the manufacturing process of the technical grade active ingredient after the majority of the toxicological testing was conducted for imidacloprid. The technical imidacloprid produced by the revised manufacturing process, termed "AMP-W", was found to be negative in the bacterial reverse mutation assay, but two of its impurities, N–[(6-chloro-3-pyridinyl)methyl] -1,2-ethanediamine (PEDA) and N, N'-bis-[6-chloro-3-pyridinyl) methyl] -1,2-ethanediamine (DIPEDA), tested positive. As the impurities were detected at trace levels (<0.1% w/w) in the technical grade active ingredient, they were not considered of toxicological concern.

Overall consideration of the toxicity of the imidacloprid mammalian metabolites indicates a low degree of concern for most of the tested compounds as they were less toxic than the parent compound. An exception to this finding involved the metabolite desnitro-imidacloprid. In vitro data suggested that this metabolite was bioactive, affecting mammalian nAChR in a manner akin to nicotine. This activity is a result of protonation of desnitro-imidacloprid under the conditions of physiological pH which in turn raises its affinity for mammalian nAChR. Desnitro-imidacloprid was more acutely toxic than imidacloprid via the oral route although the difference was only 1.4 – 2.3-fold. Guideline metabolism studies indicate this metabolite was only seen in the feces at low levels suggesting either little conversion to this metabolite in the rat or a transient presence of the metabolite.

The only in vivo data that demonstrated the presence of desnitro-imidacloprid in the brain came from a study conducted via a route of low relevance to human risk assessment (intraperitoneal). In light of the above, the potential risk to mammals from desnitro-imidacloprid is likely addressed by the risk assessment for imidacloprid.

Results of the tests conducted on laboratory animals with imidacloprid, it's metabolites and the Temprid end-use products, along with the toxicology endpoints for use in the human health risk assessment, are summarized in Appendix I, Tables 1, 2, and 3.

Incident Reports

As of 8 September 2015, there were 51 human incidents and 2000 domestic animal incidents in the PMRA database involving imidacloprid. Overall, 70% of these human and domestic animal incidents assessed for causality had at least some degree of association with exposure to the product reported in the incident. Skin effects were highly prominent in most incidents and were attributed, at least in part, to the active ingredient imidacloprid. The majority of these incidents involved direct contact with products containing 9.1% imidacloprid applied to pets. These effects are supported by the toxicology data, which indicate that imidacloprid is minimally irritating to skin.

Overall, the incidents highlight potential for skin irritation from direct contact with the concentrated product, Temprid SC Insecticide, containing imidacloprid. The product label includes the requirement for the use of chemical resistant gloves, which mitigates the potential for similar skin effects when working with the concentrated product.

3.1.1 *Pest Control Products Act* Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to take into account potential prenatal and postnatal toxicity and completeness of the data with respect to the exposure of and toxicity to infants and children. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the exposure of and toxicity to infants and children, the database contains the full complement of required studies including a multigeneration reproduction study in the rat, developmental toxicity studies in the rat and rabbit, and a developmental neurotoxicity study in the rat.

With respect to identified concerns relevant to the assessment of risk to infants and children, there was no indication of increased susceptibility in the offspring compared to parental animals in the reproduction study. In the prenatal developmental toxicity studies in rats and rabbits, developmental effects included abortions, resorptions and skeletal variations; however, these effects occurred in the presence of marked maternal toxicity (in other words, maternal deaths and body weight loss). Thus, the developmental toxicity studies provided no indication of increased susceptibility of rat or rabbit fetuses following in utero exposure to imidacloprid. In the developmental neurotoxicity study, decreases in locomotor activity and thickness of caudate/putamen as well as impaired learning on one trial in the water maze test were noted in offspring at the highest dose level tested. A NOAEL for the reduced caudate/putamen width was

not established as morphometric assessments were not performed on offspring from the low and mid dose groups. However, the concern regarding the missing measurements was low considering that i) no effects occurred in the young at lower dose levels (in particular there was no indication of adverse functional changes in the young at the low and mid dose levels); ii) the magnitude of the change in caudate/putamen width was small (2-5%); and iii) this effect occurred at a dose level that was toxic to maternal animals. Furthermore, the toxicological endpoints selected for risk assessment were considered protective of the slight brain morphometric changes. Therefore, the overall concern for this effect is low. On the basis of all the above information, the *Pest Control Products Act* factor was reduced to 1-fold.

3.2 Determination of Acute Reference Dose (ARfD)

Not required as there are no proposed food uses and contamination of drinking water sources is not expected.

3.3 Determination of Acceptable Daily Intake (ADI)

Not required as there are no proposed food uses and contamination of drinking water sources is not expected.

3.4 Occupational and Residential Risk Assessment

Occupational exposure to imidacloprid is characterized as intermediate- to long-term in duration and is predominantly by the dermal and inhalation route. Residential exposure to treated mattresses is characterised as short- to long-term and by the dermal route for adults (16+), youths (11 < 16 years) and children (1 < 2 years). Children 2 years old to < 11 years old are not assessed separately because their exposure is expected to be less than that of 1 < 2 year olds. Children (1 < 2 years) are expected to have greater exposure because of a greater body surface area (cm^2) to body-weight (kg) ratio.

3.4.1 Toxicological Endpoints

Short- term dermal:

For short- term dermal exposure assessments, the NOAEL of 8 mg/kg bw/day from the 90-day dietary study in the dog was selected. The NOAEL was based on clinical signs of neurotoxicity (trembling) and slight emaciation at the LOAEL of 22 mg/kg bw/day.

When compared to the rat, the dog was the species most sensitive to neurotoxic effects after short-term exposure. Although no effects were observed up to the limit dose in a 21-day rabbit dermal toxicity study with imidacloprid, this study did not include any specific assessments for neurotoxicity, such as a functional observational battery (FOB). In oral neurotoxicity studies in the rat, effects on more detailed analyses of neurotoxicity (such as the FOB, motor activity testing, and learning and memory) were noted but at higher doses than the clinical signs of trembling noted in the dog. As such, the 21-day dermal study in the rabbit was not considered suitable for use in the dermal risk assessment.

Short-term inhalation:

For short-term inhalation exposure assessments, the NOAEL of 8.4 mg/kg bw/day from the 28-day inhalation study in the rat was selected. The NOAEL was based on liver effects and increased coagulation time at the LOAEL of 51.8 mg/kg bw/day.

Intermediate-term dermal and inhalation:

For intermediate-term dermal and inhalation exposure assessments, the NOAEL of 8 mg/kg bw/day from the 90-day dietary study in the dog was selected. As previously discussed, the dermal toxicity study was deemed unsuitable for use in the dermal risk assessment. As there was uncertainty as to whether toxicity increased with duration of dosing following inhalation exposure, the inhalation toxicity study was also deemed unsuitable for scenarios other than short-term. Accordingly, an oral study was used for risk assessment in lieu of appropriate route-specific studies.

Long-term dermal and inhalation:

For long-term dermal and inhalation scenarios, the NOAEL of 5.7 mg/kg bw/day from the 2-year rat study was selected. At the LOAEL of 17 mg/kg bw/day, an increased incidence of mineralized particles in the colloid of isolated thyroid follicles was observed in males.

Incidental (non-dietary) oral ingestion (short-term):

For non-dietary (incidental) scenarios of short or intermediate duration, the NOAEL of 8 mg/kg bw/day from the 90-day dietary study in the dog was selected for risk assessment as the route and duration of study were deemed appropriate.

For all scenarios (occupational and residential), routes (dermal, inhalation and non-dietary) a target Margin of Exposure (MOE) of 100 to account for intraspecies variation and interspecies extrapolation is considered appropriate. In addition, the *Pest Control Products Act* factor has been reduced to 1-fold for residential assessments.

The endpoints and target MOE selected for risk assessment provide adequate margins to other endpoints of concern, including the changes in brain morphometrics in rat offspring in the DNT study.

3.4.1.1 Dermal Absorption

A dermal absorption value of 5% was chosen based on a previously reviewed rat in vivo dermal absorption study.

3.4.2 Occupational Exposure and Risk

Mixer/loader/applicator Exposure and Risk Assessment

Exposure to Pest Control Operators (PCOs) during mixing, loading, application, clean-up and repair is expected to be intermediate- to long-term in duration and to occur primarily by the dermal and inhalation routes.

Chemical-specific data for assessing PCO exposures during pesticide handling activities were not submitted. Therefore, dermal and inhalation exposure estimates for workers mixing, loading, and/or applying imidacloprid to mattresses using a manually pressurized sprayer or an aerosol bag-on-valve container were generated from the Pesticide Handlers Exposure Database (PHED) version 1.1. The exposure estimates are based on a PCO wearing a single layer, long-sleeved shirt and long pants, plus chemical-resistant gloves.

Dermal exposure was estimated by combining the unit exposure values with the amount of product handled per day and the dermal absorption value of 5%. Inhalation exposure was estimated by combining the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using 80 kg adult body weight.

Exposure estimates were compared to the toxicological endpoint or NOAEL (no observed adverse effects levels) to obtain the margin of exposure (MOE); the target MOE is 100. All calculated MOEs exceeded the target MOE of 100 (Appendix I, Table 4) and thus, exposure to mixer/loader/applicator or applicator is not expected to result in risks of concern when imidacloprid is used according to label directions.

3.4.2.2 Post-Application Worker Exposure and Risk

There is potential for exposure to workers re-entering areas treated with imidacloprid. However, it is expected to be less than the exposure to PCOs mixing, loading and/or applying which already exceeds the target MOE. It is expected that workers re-entering treated areas will be wearing long sleeves, long pants and shoes plus socks.

3.4.3 Residential Exposure and Risk Assessment

3.4.3.1 Post-Application Exposure and Risk

A single post-application dermal risk assessment is presented for both end-use products as their application rates are similar and exposure scenarios are identical. Only dermal exposure from the major new use for imidacloprid as a mattress treatment were calculated for adults (16+), youth (11 < 16 years) and children (1 < 2 years). Exposure to children 2 years old to < 11 years old was not assessed separately because their exposure is expected to be less than that of 1 < 2 year olds. Children (1 < 2 years) are expected to have greater exposure because of greater body surface area (cm^2) to body-weight (kg) ratio.

Short-term exposure to treated mattresses was calculated. The treatment of bed bugs can potentially be long-term in duration; however, long-term exposure was not calculated separately because the dermal endpoints are similar for the short- and long-term exposure durations and the route of exposure in the toxicological studies is the same. Also, exposure parameters for long-term assessments use more conservative values, such as 50^{th} percentile, in comparison to short-term assessments, which use the arithmetic mean or 90^{th} percentile. As such, short-term risk assessments are representative of any potential long-term risk.

Exposure and risk were calculated assuming only the tufts and seams of the mattress were treated.

All default values were derived from the 2012 United States Environmental Protection Agency Residential SOP for Indoor Environments (Section 7). Exposure to imidacloprid exceeded the target MOE of 100 for use on mattresses (Appendix I, Table 5) and thus, post-application exposure is not expected to result in risks of concern when imidacloprid is used according to label directions.

3.4.3.2 Bystander Exposure and Risk

The end-use product labels specifically state that no one is to be present during application, therefore bystander exposure is expected to be negligible

3.5 Aggregate Risk Assessment

3.5.1 Toxicology Endpoints

For short- and intermediate-term aggregate risk assessment the NOAEL of 8 mg/kg bw/day from the 90-day dietary study in the dog was selected. At the LOAEL of 22 mg/kg bw/day, clinical signs of neurotoxicity (trembling) were observed during the first week of dosing, as was slight emaciation. These effects were considered relevant to all routes of exposure (oral, dermal and inhalation) and all sub-populations. Although liver toxicity was also a common endpoint across various routes of exposure, it was not selected for aggregation as the neurotoxicity endpoint was considered protective of liver effects. A target MOE of 100 to account for intraspecies variation and interspecies extrapolation is considered appropriate.

For long-term aggregate risk assessment, the NOAEL of 5.7 mg/kg bw/day from the 2-year dietary study in the rat was selected. At the LOAEL of 17 mg/kg bw/day, an increased incidence of mineralized particles in the colloid of isolated thyroid follicles was observed in males. These effects were considered relevant to all routes of exposure (oral, dermal and inhalation) and all sub-populations. A target MOE of 100 to account for intraspecies variation and interspecies extrapolation is considered appropriate.

3.5.2 Aggregate Exposure and Risk

The chronic dietary exposure for imidacloprid for a child (1 < 2 years) is 0.014453 mg/kg bw/day. Aggregate exposure was only assessed for this age group because the body surface area to weight ratio is higher than any other age group. Dermal exposure was aggregated with the dietary exposure resulting in an MOE exceeding the target MOE of 100 (Appendix I, Table 6).

3.6 Cancer Assessment

There was no evidence of carcinogenicity and therefore, no cancer risk assessment is necessary.

3.7 Cumulative Assessment

The *Pest Control Products Act* requires the Agency to consider the cumulative effects of pest control products that have a common mechanism of toxicity. Imidacloprid belongs to a group of insecticides commonly known as the neonicotinoids. Upon completion of the re-evaluation of imidacloprid, it will be determined whether a cumulative effects assessment is necessary and if so, this will be performed with all relevant chemicals of the common mechanism group.

4.0 Value

4.1 Consideration of Benefits

Bed bugs are difficult to control insects that have substantial impacts on the well-being of people. There are few insecticides that can be applied to human proximal sites such as mattresses to kill bed bugs. Pyrethrins (MOA 3A) are conventional insecticides and silicon dioxide present as diatomaceous earth is a non-conventional insecticide that may be applied to these locations to kill bed bugs. The combination of beta-cyfluthrin (MOA 3A) and imidacloprid (MOA 4A) improved the efficacy against pyrethroid resistant bed bugs compared to beta-cyfluthrin or imidacloprid alone. In addition, this combination of insecticides also kills bed bug eggs on contact. These products can be used in conjunction with other pest management practices such as laundering linens, steam cleaning, mattress and box spring encasements and bed bugs monitoring traps.

4.2 Effectiveness Against Pests

Temprid SC Insecticide:
Based on efficacy data from five studies, a claim of "kills on contact" was supported for bed bugs. The data demonstrated improved efficacy when using the combination of the imidacloprid and beta-cyfluthrin compared to either insecticide alone. It also demonstrated that the products would kill all life stages of bed bugs (eggs, nymphs and adults).

Temprid ReadySpray:
Based on extrapolation of the value information assessed for Temprid SC Insecticide, a claim of "kills on contact" was supported for all life stages of bed bugs.

4.3 Non-Safety Adverse Effects

The following cautionary statement is located on the labels of Temprid SC Insecticide and Temprid ReadySpray: "Users should test a small, inconspicuous area first to ensure there are no adverse effects such as staining, discolouration or corrosion prior to treating an entire area."

4.4 Supported Uses

Temprid SC Insecticide diluted to 1 mL product per L of water kills bed bugs on contact. Temprid ReadySpray is a ready-to-use formulation that kills bed bugs on contact. Both products kill all life stages of bed bugs (that is, eggs, nymphs and adults).

5.0 Pest Control Product Policy Considerations

5.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment.

The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy: persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

The Toxic Substances Management Policy (TSMP) was assessed previously in Regulatory Note REG2001-11, Imidacloprid and Regulatory Note R97-01, Admire. No new information on imidacloprid was submitted with this data package that would affect the previous assessment.

- Imidacloprid does not meet Track 1 criteria, and is not considered a Track 1 substance.
- Imidacloprid is not expected to form any transformation products that are Track 1

5.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[14]. The list is used as described in the PMRA Notice of Intent NOI2005-01[15] and is based on existing policies and regulations including DIR99-03 and DIR2006-02[16], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- The end-use product Temprid SC Insecticide and Temprid ReadySpray do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette.*

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

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14 *Canada Gazette, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern and in the order amending this list in the Canada Gazette, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

15 *NOI2005-01, List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

16 *DIR2006-02, Formulants Policy and Implementation Guidance Document.*

6.0 Summary

6.1 Human Health and Safety

The toxicology database submitted for imidacloprid is adequate to define the majority of toxic effects that may result from exposure. In subchronic and chronic studies on laboratory animals, the primary targets were the liver, kidney, thyroid gland, eye and nervous system. There was no evidence of carcinogenicity in rats or mice after long-term dosing. There was no evidence of increased susceptibility of the young in reproduction or developmental toxicity studies.

PCOs handling Temprid SC Insecticide or Temprid ReadySpray are not expected to be exposed to levels of imidacloprid that will result in risks of concern when the products are used according to label directions. The personal protective equipment of a long-sleeved shirt, long pants, chemical-resistant gloves and shoes plus socks is adequate.

Exposure to individuals contacting treated surfaces is not expected to result in risks of concern when imidacloprid is used according to label directions. Mattresses must be dry before clean linens are replaced.

6.2 Value

Temprid SC Insecticide and Temprid ReadySpray combine two insecticides, a pyrethroid and neonicotinoid, to kill bed bugs. Imidacloprid is registered for a variety of uses, including ant baits and cockroach baits but human proximal sites such as mattresses are a new use site for this active ingredient. The combination of these two insecticides improves the efficacy against pyrethroid-resistant bed bugs compared to either insecticide alone. Further, these products kill bed bugs at all life stages.

7.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use Bay NTN 33893 Technical Insecticide and its end-use products, Temprid SC Insecticide and Temprid ReadySpray Insecticide, containing the technical grade active ingredient imidacloprid. The end-use products are coformulated with beta-cyfluthrin to kill bed bugs in sites such as mattresses.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

↑	increased
↓	decreased
µg	microgram(s)
♀	females
♂	males
a.i.	active ingredient
AChE	acetylcholinesterase
AChR	acetylcholine receptor
AD	administered dose
ADI	allowable daily intake level
ALP	alkaline phosphatase
ALT	alanine transaminase
AOX	aldehyde oxidase
ARfD	acute reference dose
AST	aspartate aminotransferase
BChE	brain cholinesterase
BUN	blood urea nitrogen
bw	body weight
bwg	body weight gain
CAF	Composite Assessment Factor
CAT	catalase
CXB	imidacloprid
DE	Diatomaceous earth
DNIMI	desnitro-imidacloprid
ECG	electrocardiogram
EChE	erythrocyte cholinesterase
EP	end-use product
ER	endoplasmic reticulum
F_0	parental generation
F_1	first filial generation
F_2	second filial generation
fc	food consumption
FOB	functional observational battery
FSH	follicle-stimulating hormone
GD	gestation day
GFAP	glial fibrillary acidic protein
GGT	gamma-glutamyl transpeptidase
GI	gastrointestinal
GLDH	glutamate dehydrogenase

GPx	glutathione peroxidase
GSH	glutathione
GST	glutathione s-transferase
h	hour(s)
HED	Health Evaluation Directorate
Hg	mercury
hr(s)	hour(s)
HtM	Hand-to-mouth
i.p.	intraperitoneal
IL	interleukin
iNOS	inflammatory nitric oxide synthase
IRAC	Insecticide Resistance Action Committee
iv	intravenous
kg	kilogram(s)
kgbw	kilograms of bodyweight
L	litre(s)
LC_{50}	median lethal concentration
LD	lactation day
LD_{50}	median lethal dose
LH	luteinizing hormone
LOAEL	lowest observed adverse effect level
M/L/A	Mixer/loader/applicator
MAS	maximum average score
MDA	malondialdehyde
MFO	mixed-function oxidase
mg	milligram(s)
mg/kg bw/day	Milligrams per kilogram of bodyweight per day
min	minute(s)
MIS	mean irritation score
mL	millilitre(s)
mm	millimitre(s)
MOA	mode of action
MOE	margin of exposure
MOE	Margin of exposure
mRNA	messenger ribonucleic acid
nAChR	neuronal acetylcholine receptor
NADPH	nicotinamide adenine dinucleotide phosphate
ng	nanogram(s)
nNOS	neuronal nitric oxide synthase
NOAEL	no observed adverse effect level
NOAEL	No observed adverse effect level

NOS	nitric oxide sythase
PChE	plasma cholinesterase
PCO	Pest Control Operator
PHED	Pesticide Handlers Exposure Database
PMRA	Pest Management Regulatory Agency
PND	post-natal day
ppb	parts per billion
PPE	Personal protective equipment
ppm	parts per million
rel	relative
RER	rough endoplasmic reticulum
RNA	ribonucleic acid
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SOD	super oxide dismutase
T3	triiodothyronine
T4	thyroxine
TC	Transfer coefficient
TNF	tumor necrosis factor
TSH	thyroid stimulating hormone
USC	Use-site category
wt(s)	weight(s)

Appendix I Tables and Figures

Table 1 Toxicity Profile of Imidacloprid

NOTE: Effects noted below are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Effects on organ weights are known or assumed to reflect changes in absolute weight and relative (to bodyweight) weight unless otherwise noted

Study Type/ Animal/ PMRA#	Study Results
TOXICOKINETICS (PMRA# 1155769, 1155781, 1155782, 2030947)	
Investigations into the toxicokinetic behaviour of imidacloprid were conducted using the parent compound radio-labelled at either the methylene or imidazolidine position. **Rate and extent of absorption and excretion:** Both methylene-labelled imidacloprid ([Methylene-^{14}C] Imidacloprid) and imidazolidine-labelled imidacloprid ([Imidazolidine-4,5-^{14}C] Imidacloprid) were rapidly absorbed with approximately 90% of the administered dose (AD) being eliminated within 24 hours. There were no biologically significant differences between sexes, dose levels, or routes of administration. Urinary excretion was the major route of elimination regardless of radio-label position (70-91% of AD), with a lesser amount eliminated in faeces (7-25% of AD). Biliary excretion was a major contributor to faecal radioactivity; only 5% of AD was excreted in faeces in bile-fistulated animals administered the methylene-labelled compound. Only a trace amount was excreted in expired air regardless of radio-label position. For methylene-labelled imidacloprid, the maximum plasma concentration occurred between 1.1 and 2.5 hours, and elimination half-lives were 3 and 26-118 hours. For imidazolidine-labelled compound, the maximum plasma concentratio241ns were measured between 1 and 4 hours, and elimination half-lives ranged between 9 and 25 hours. Methylene-labelled nitrosimine, a nitroso derivative of imidacloprid formed during pretreatment (chronic oral dosing), showed a toxicokinetic pattern similar to that of methylene-labelled imidacloprid. However, more radioactivity was found in tissues of those animals receiving methylene-labelled imidacloprid (0.9%-3.4% of AD) than those receiving methylene-labelled nitrosimine (0.2% of AD). **Distribution / target organ(s):** Total tissue burden of methylene-labelled imidacloprid after 48 hours accounted for approximately 0.5% of the AD, with major sites of accumulation being the liver, kidney, lung, skin, and plasma and minor sites being the brain and testes. Total tissue burden of imidazolidine-labelled imidacloprid accounted for approximately 1% of the AD, with the major sites being the liver, kidney, lung, and skin and the minor sites being the brain and muscle. The major sites of accumulation for methylene-labelled nitrosimine included the lung, renal fat, liver, and kidney, with minor sites being the testes and brain. **Biotransformation:** These studies identify two main routes of metabolism responsible for the degradation of imidacloprid. The first involves hydroxylation of the imidazolidine ring followed by oxidative cleavage to yield 6-chloronicotinic acid and its glycine conjugate. Dechlorination of this metabolite produces 6-hydroxynicotinic acid and its mercapturic acid derivative. Hydroxylation of the imidazolidine ring can also be followed by the elimination of water to give an olefinic metabolite. The second pathway involves nitroreduction to yield nitrosimine, amino-guanidine derivatives and desnitro-imidacloprid. Desnitro-imidacloprid undergoes oxidative cleavage to imidazolidine and 6-chloronicotinic acid and its glutathione conjugates.	

Study Type/ Animal/ PMRA#	Study Results
Neonicotinoid nitroreductase identification in rabbit liver cytosol PMRA# 2418100	Supplemental As part of the metabolic pathway, imidacloprid undergoes nitroreduction to form nitrosoguanidine and aminoguanidine. The molybdo-flavoenzyme aldehyde oxidase (AOX) was identified as the neonicotinoid nitroreductase in rabbit liver cytosol. Large species differences are observed in imidacloprid nitroreductive activity of liver cytosol. Nitroreduction to aminoguanidine was high in rabbit, moderate in monkey, human and rat and low in mouse, cow, dog, cat and chicken. Nitroreduction to nitrosoguanidine was moderate in all species except dog, cat and chicken (low).
In vitro metabolism in Human P450 Supersomes (baculovirus infected insect cells containing human P450 cDNA) PMRA# 2418124	Supplemental Principal organoextractable NADPH-dependent metabolites are the 5-hydroxy (major) and olefin (minor) derivatives from hydroxylation and desaturation of the imidazolidine moiety and the nitrosoimine (major), guanidine (minor) and urea (trace) derivatives from reduction and cleavage of the nitroimine substituent. Isoenzyme activity selective for imidazolidine oxidation: CYP3A4>CYP2C19 or CYP2A6>CYP2C9. Isoenzyme activity selective for nitrosimine reduction: CYP1A2>CYP2B6> CYP2D6>CYP2E1. Flavin monooxygenases not active.
Absorption in human intestinal CaCo-2 cell line PMRA# 2418098	Supplemental Imidacloprid crossed the transepithelial layer very quickly and completely. Data suggests imidacloprid strongly absorbed by inward and outward active transporters.
Metabolism in Swiss Webster mice (intraperitoneal) PMRA# 2418108	Supplemental Peak levels of imidacloprid at 15 min post-dosing in brain (6 ppm) liver (18 ppm) and plasma (8 ppm), half-life was 90, 30 and 80 min in brain, liver and plasma, respectively.Liver metabolites included desnitro-imidacloprid, nitrosimine-imidacloprid, aminoguanidine-derivative, methyltriazinone derivative of aminoguanidine, olefin-imidacloprid, 5-hydroxy-imidacloprid and 4,5-dihydroxy-imidacloprid. Brain metabolites included desnitro-imidacloprid and nitrosimine-imidacloprid. Plasma metabolites included nitrosimine-imidacloprid, olefin-imidacloprid and 5-hydroxy-imidacloprid. Urine (0-24 hr) contained imidacloprid (22%) and 5-hydroxy-imidacloprid (22%) and lesser metabolites (<5%). Feces (0-24 hr) had <0.01% of administered dose.
Metabolism (i.p. dosing) ♂ Swiss Webster mice ♂ DBA2 mice ♂ CD-1 mice PMRA# 2418126	Supplemental; i.p. dosing ↓ nitrosimine-imidacloprid and desnitro-imidacloprid in Swiss Webster mice with chemically-reduced (tungsten or hydralazine) AOX activity and in AOX-deficient DBA2 mice.

Study Type/ Animal/ PMRA#	Study Results
Blood and coat residue study (single dermal application) Dog PMRA# 2417849	Supplemental; 9.1% pure (Advantage formulation) **364 mg/dog:** Blood and glove wipe samples were collected from dogs 24h, 72h and then weekly for 5 weeks post application. Peak imidacloprid residues were detected in blood (54 ppb) and gloves (254 ppm) at 24h post-application. Residues detected in blood at 72h post-application were 19 ppb, and were not detected after1 week post-application. Residues detected in glove samples were low by the 4th week (0.08 ppm) and not detected by the 5th week.
ACUTE STUDIES - Technical Imidacloprid	
Oral Wistar rat PMRA# 2030939	LD_{50} (♂) = 642 mg/kg bw; LD_{50} (♀) = 648 mg/kg bw Clinical signs included apathy, staggering or spastic gait, labored breathing, spasms or transient spasms, transient tremors, decreased motility, increased water intake, diuresis, piloerection, hypersalivation, absence of feces and transient convulsions. **MODERATE TOXICITY**
Oral Wistar rat PMRA# 2030940	LD_{50} (♂) = 504 mg/kg bw; LD_{50} (♀) = 379 mg/kg bw Clinical signs included apathy, staggering and spastic gait, labored breathing, reduced motility, spasmodic state (periodic in some cases), periodic tremors, soft feces and piloerection. **HIGH TOXICITY**
Oral Wistar rat PMRA# 1155724	LD_{50} (♂) = 424 mg/kg bw; LD_{50} (♀) = 450-475 mg/kg bw Clinical signs at ∃ 100 mg/kg bw (♂) or 250 mg/kg bw (♀): 9 motility, apathy, breathing disturbances, staggered gait, narrowed palpebral fissures, transient trembling and/or spasms (resolved 2-6 days). **HIGH TOXICITY**
Dermal Wistar rat PMRA# 1155729	LD_{50} (♂/♀) > 5000 mg/kg bw No clinical signs of toxicity or abnormal findings at necropsy; 9 bwg (♀). **LOW TOXICITY**
Inhalation Wistar rat PMRA# 1155720	LC_{50} (♂/♀) > 0.069 mg/L (Aerosol) LC_{50} (♂/♀) > 5.32 mg/L (Dust) Clinical signs in rats exposed to dust for 4 hours at ∃ 2.58 mg/L: laboured breathing, decreased motility, piloerection; slight tremors were noted 1-2 hrs post-dosing at 5.32 mg/L; signs resolved by day 1. **LOW TOXICITY**

Study Type/ Animal/ PMRA#	Study Results
Eye Irritation NZW Rabbit PMRA# 1155731	MAS = 0 MIS = 6 at 1 hr **Minimally irritating**
Dermal Irritation NZW Rabbit PMRA# 1155733	MAS = 0 MIS = 1 at 1 hr **Non-irritating**
Skin Sensitization-(Maximization) Hartley Guinea pig PMRA# 1155747	**Not a dermal sensitizer**
ACUTE STUDIES – Desnitro-imidacloprid (mammalian metabolite)	
Oral Sprague Dawley rat PMRA# 2030936	LD_{50} (♂) = 300 mg/kg bw; LD_{50} (♀) = 280 mg/kg bw Clinical signs ≥ 95 mg/kg bw included sedation, ptosis, abnormal respiration, abnormal gait, tremors (both sexes) **HIGH TOXICITY**
ACUTE STUDIES – Urea-imidacloprid (mammalian metabolite)	
Oral Sprague Dawley rat PMRA# 2030937	LD_{50} (♂) = 4080 mg/kg bw; LD_{50} (♀) = 1820 mg/kg bw Clinical signs included mydriasis, abnormal gait, sedation, nasal bleeding, abnormal respiration, salivation,tremors **SLIGHT TOXICITY**
ACUTE STUDIES – Olefin-imidacloprid (mammalian metabolite)	
Oral Sprague Dawley rat PMRA# 2030938	LD_{50} (♂) = 3500 mg/kg bw; LD_{50} (♀) = 1100 mg/kg bw Clinical signs ≥ 440/200 mg/kg bw included mydriasis, tremors, abnormal respiration, lacrimation, red tears, emaciation, abnormal gait, red urine and piloerection **SLIGHT TOXICITY**
ACUTE STUDIES – Nitrosimine-imidacloprid (mammalian metabolite)	
Oral Sprague Dawley rat PMRA# 2417845	LD_{50} (♂) = 1980 mg/kg bw; LD_{50} (♀) = 3560 mg/kg bw Clinical signs at ∃ 980 mg/kg bw included mydriasis, tremors, sedation, exophthalmos, abnormal respiration, convulsions, red lacrimation, nasal bleeding, emaciation, and/or abnormal gait. All signs resolved by day 9. **HIGH TOXICITY**

Study Type/ Animal/ PMRA#	Study Results
SHORT TERM TOXICITY	
21-day dermal NZW rabbit PMRA# 1155690	NOAEL > 1000 mg/kg bw/day; LOAEL not established There were no treatment-related findings.
28-day inhalation Wistar rat PMRA# 1155689	NOAEL = 0.031 mg/L (equivalent to 8.4 mg/kg bw/day) No mortalities; no clinical signs of toxicity. **0.031 mg/L (8.4 mg/kg bw/day)** - ↕ hepatic MFO activity (♀) considered non-adverse. **0.191 mg/L (51.8 mg/kg bw/day)** - ↕ GLDH, ↕ triglyceride , ↕ MFO; ↕ cytochrome P450 (♂);↕ liver wt, ↕ AST, ↕ ALT, ↕ ALP, ↕ coagulation time (♀).
96-day dietary Wistar rat PMRA# 1155682	NOAEL = 150 ppm (14/20.3 mg/kg bw/day; ♂/♀) **≥600 ppm (60.9/83.3 mg/kg bw/day):** ↕ calcium; ↕ bw (♂); ↕ total leukocytes (♀). **2400 ppm (300/422 mg/kg bw/day):** ↕ bwg, ↕ fc, ↕ water intake, ↕ food conversion efficiency, ↕protein, ↕albumin, ↕bilirubin, and ↕platelets, ↕ ALP, ↕ thromboplastin time, ↕ brain cholinesterase activity; single cell and focal necrosis, inflammatory infiltration, cytoplasmic transformation swollen nuclei in liver, ↕ ALT, ↕ AST, ↕ BUN, ↕ blood creatinine, ↕ urinary protein, ↕ protein/ creatinine ratio, ↕ triglycerides, ↕ cholesterol, ↕ urinary creatinine (♂);↕ bw (♀). **Recovery group:** ↕ bw, ↕ fc, ↕ protein, ↕ thromboplastin time, ↕ brain cholinesterase activity
4-week dietary Beagle dog Range-finding PMRA# 1155691	Supplemental. NOAEL not established. **≥1000 ppm (31 mg/kg bw/day):** transient ↕ in fc, ↕ cytochrome P450 (not assessed at higher dose), hepatocellular hypertrophy, pigmentation of the Kupffer cells, thyroid follicular atrophy; ↕ liver wt in one ♀. **5000 ppm (49 mg/kg bw/day):** all animals died or sacrificed moribund (1 ♂ died day 2, 1 ♀ died day 18, 2/sex sacrificed day 24), vomiting, ataxia, tremors, body weight loss, ↕ fc, ↕ BUN, ↕ bilirubin, ↕ GGT, ↕ triglycerides, ↕ lipids, ↕ ALP, ↕ ∀-1 globulin, ↕T3, reddening, congestion, and discolouration of GI tract, red-brown cysts and valvular telangiestasis in the heart, ↕ zymogen content in the pancreas, tubular degeneration in the testes, thymic involution, acinar atrophy of the salivary gland, bone marrow atrophy.

Study Type/ Animal/ PMRA#	Study Results
90-day dietary Beagle dog PMRA# 1155681	NOAEL = 200 ppm (7.7/8.0 mg/ kg bw/day; ♂/ ♀) **600 ppm (22.1/24.8 mg/kg bw/day):** trembling (all animals first week of dosing) and slightly emaciated animals. **1800-1200 ppm (45.0/45.7 mg/kg bw/day):** trembling (all animals week 1 to 5) and severe tremors (all animals week 1, 1 ♀ week 3), ↓ fc and water consumption (1st 3 weeks), emaciated animals and decreased urinary volumes. No effect on thyroid pathology, TSH, T3 or T4
12-month dietary Beagle dog PMRA# 1155758	NOAEL > 1200- 2500 ppm (40-72/42-72 mg/kg bw/day; ♂/ ♀) LOAEL not established **1200-2500 ppm (40-72 mg/kg bw/day):** non-adverse findings: transient ↓ in fc, ↑ hepatic cytochrome P450 (not assessed at lower doses); ↑ cholesterol (♀). No effect on thyroid pathology. A 2-week follow-up study, designed to resolve discrepancies between 90-day and 12-month studies, revealed no clinical signs (no trembling) in 2/dogs/sex dosed at 1200 ppm.
SHORT TERM TOXICITY – Nitrosimine-imidacloprid (mammalian metabolite)	
12-week drinking water Wistar Bor rat PMRA# 1155695	NOAEL = 100 ppm (13 mg/kg bw/day) **300 ppm (35/39 mg/kg bw/day):** Final sacrifice: ↓ lymphocytes and ↑ polymorphonuclear cells **1000 ppm (106/117 mg/kg bw/day):** ↑ water intake Interim sacrifice: ↓ thymus wt, ↑ relative heart and kidney wt (♂); ↑ thromboplastin time,↓ relative spleen wt (♀) Final sacrifice: ↑ relative kidney wt; ↓ absolute liver wt, ↓ adrenal gland wt (♂); ↓ sodium, ↑ reticulocyte count,↓ spleen wt (♀)
CHRONIC TOXICITY AND ONCOGENICITY	
2-year dietary Wistar rat PMRA# 1155757, 1155760, 1155761	NOAEL = 100 ppm (5.7 mg/kg bw/day)(♂); 300 ppm (24.9 mg/kg bw/day)(♀) **≥300 ppm (16.9 mg/kg bw/day):** ↑ incidence of mineralized particles in colloid of isolated thyroid follicles (♂). **≥900 ppm (51.3/73.0 mg/kg bw/day):** ↓ bw; ↑ incidence of mineralized particles in colloid of isolated thyroid follicles, ↓ bwg (♀). **1800 ppm (103/144 mg/kg bw/day):** ↑ thyroid colloid aggregation, ↑ incidence of renal nephropathy, ↑ urine protein; ↑ retinal atrophy, ↑ porphyrin accumulation in Harderian glands (♀). No effect on TSH, T3 or T4. **Not oncogenic.**

Study Type/ Animal/ PMRA#	Study Results
2-year dietary B6C3F1 mouse PMRA# 1155697, 1155705	NOAEL = 1000 ppm (208/272 mg/kg bw/day; ♂/♀) **≥1000 ppm (208/274 mg/kg bw/day):** non-adverse findings - sporadic 9 fc; 9 bwg (♂); 9 water intake (♀). **2000 ppm (414/424 mg/kg bw/day):** 8 incidence of squeaking and twittering, 9 bw after week 13, 9 bwg, water consumption, 9 fc (♂); 9 food conversion efficiency, 9 liver and spleen wt (♀). **Not oncogenic.**
REPRODUCTION AND DEVELOPMENTAL TOXICITY	
Multi-generation dietary Wistar rat PMRA# 1155687, 1155688	**Parental** NOAEL = 250 ppm (16.5/18.9 mg/kg bw/day; ♂/♀) **700 ppm (47.3/ 52.3 mg/kg bw /day):** 9 bwg during premating (F_0), 8 demethylase activity; 9 bwg (F_1 ♀) during premating, 1st gestation, and 2nd gestation; 8 bwg during lactation ($F_{1A/B}$, $F_{2A/B}$); 8 cytochrome P450 content (♂); 9 fc (♀). **Reproductive** NOAEL > 700 ppm (47.3/52.3 mg/kg bw/day) LOAEL not established. No treatment-related findings. **Offspring** NOAEL = 250 ppm (18.9 mg/kg bw/day) **700 ppm (52.3 mg/kg bw/day):** 9 pup wt during lactation ($F_{1A/B}$, $F_{2A/B}$). Note: study report dated 1990 - limited organ weights (liver, ovaries, testes), no sperm assessment, no ovarian follicle counts.
Developmental toxicity Sprague Dawley rat PMRA# 1155698	**Maternal** NOAEL = 10 mg/kg bw/day **30 mg/kg bw/day:** 9 bwg GD 6-11 and 6-16, 9 corrected bwg GD 6-21, 9 fc GD 6-11. **100 mg/kg bw/day:** 9 bwg, 9 corrected bwg GD 6-21, 9 fc during treatment, 8 fc post-dosing. **Developmental** NOAEL = 30 mg/kg bw/day **100 mg/kg bw/day:** slight 8 in incidence of wavy ribs. **No evidence of sensitivity of the young.**

Study Type/ Animal/ PMRA#	Study Results
Developmental toxicity - Range-finding Chinchilla rabbit PMRA# 2428119	Supplemental. NOAEL not established. **Maternal** **≥50 mg/kg bw/day:** 9 bw and fc. **100 mg/kg bw/day:** 8 post-implantation loss, markedly 9number of live fetuses per dam **Developmental** **≥50 mg/kg bw/day:** 9 fetal wt. **100 mg/kg bw/day:** markedly 9number of live fetuses per dam
Developmental toxicity Chinchilla rabbit PMRA# 1155699	**Maternal** NOAEL = 8 mg/kg bw/day **24 mg/kg bw/day:** transient 9 bwg and fc during dosing. **72 mg/kg bw/day:** 2 unscheduled deaths (GD 18, 19), 1 abortion (GD 26), 2 total litter resorptions, 9 bw GD 17-21, 9 bwg, body weight loss during dosing, 9 fc during treatment and post-dosing, 8 late resorptions,8 postimplantation loss, 9 number of live fetuses/litter. **Developmental** NOAEL = 24 mg/kg bw/day **72 mg/kg bw/day:** 1 abortion (GD 26), 2 total litter resorptions,8 late resorptions, 8 postimplantation loss, 9 number of live fetuses/litter, 9 litter weights,9 fetal wt (more pronounced in ♀), slight 8 in skeletal malformations (fused, asymmetric, missing and abnormally ossified sternebrae, shortened tail) - total of 5/83 fetuses (3/11 litters) versus 0/136 (0/16) in controls. **Evidence of malformations at maternally-toxic dose.**
NEUROTOXICITY	
Acute neurotoxicity Sprague Dawley rat PMRA# 1039613, 1039650	NOAEL (♂) = 42 mg/kg bw; NOAEL (♀) not established **≥42 mg/kg bw:** 9 motor and locomotor activity days 0, 7 and 14 (♀). **≥151 mg/kg bw:** tremors; red nasal staining, 9 motor and locomotor activity day 0 (♂). **307 mg/kg bw:** mortalities day 0-1, clinical signs days 0-1 (tremors, uncoordinated gait, 9 activity, coolness to touch, nasal staining), findings noted days 0-5 included: 9 number of rears, 9 grip strength (forelimb and hindlimb), 9 response to stimuli (auditory, touch, tail pinch), 8 gait abnormalities, 8 righting reflex impairments, and 9 body temperature; 9 motor and locomotor activity days 7 and 14, 9 absolute brain wt (♂) No neuropathology findings. **20 mg/kg bw (♀; supplemental study):** 9 motor and locomotor activity days 0, 7 and 14 (♀).

Study Type/ Animal/ PMRA#	Study Results
13-week neurotoxicity Fischer rat PMRA# 1039643, 1039652, 259324	NOAEL = 150 ppm (9.3/10.5 mg/kg bw/day; ♂/♀) **≥1000 ppm (63.3/ 69.3 mg/kg bw/day):** 9 bwg (first 4 weeks), 9 terminal bw; 9 forelimb grip strength (♂). No neuropathology findings.
Developmental neurotoxicity (2001) Wistar rat PMRA# 591475	**Maternal** NOAEL = 20 mg/kg bw/day **750 ppm (55 mg/kg bw/day)**: 9 bwg LD 0-7, 9 fc week 3 of gestation and week 1 of lactation. **Offspring** NOAEL = 20 mg/kg bw/day **750 ppm (55 mg/kg bw/day):** 9 bw before weaning and after weaning with recovery (♀) by PND 50; 9 bwg during lactation with recovery by PND 17; 9 overall locomotor activity on PND 17 and 21 (♀); 8 in errors and time to complete trial 1 in session 1 of water maze testing at study termination (♂); 9 thickness of caudate/putamen (♀; only assessed at the high-dose).
GENOTOXICITY	
Gene mutations in bacteria Salmonella typhimurium strains TA 98, TA 100, TA 1535 and TA 1537; E. Coli WP2uvrA PMRA# 1155714	**Negative** up to 5000 µg/plate with and without activation
Gene mutations in bacteria Salmonella typhimurium strains TA 98, TA 100, TA 1535 and TA 1537 PMRA# 1155710	**Negative** up to 12,500 µg/plate with and without activation
Gene mutations in mammalian cells in vitro Chinese hamster ovary cells (HGPRT locus) PMRA# 1155706	**Negative** up to 125 :g/ mL without activation and 1222 µg/mL with activation

Study Type/ Animal/ PMRA#	Study Results
Chromosome aberration in vivo Chinese hamster PMRA# 1155701	**Negative**
Chromosome aberration in vivo NMRI mice (♂) PMRA# 1155700	**Negative** 2/10 died at 100 mg/kg bw in a pilot study.
Chromosome aberrations in vitro Human lymphocyte cells PMRA# 1155711	**Positive** at 500 µg/mL without activation and 1300 µg/mL with activation, both toxic doses
Micronucleus assay in vivo Bor:NMRI (SPF Han) mouse PMRA# 1155755	**Negative** 2/ 10 died in a pilot study at 100 mg/kg bw.
Sister chromatid exchange in vivo Chinese hamster PMRA# 1155693, 1155694	**Negative**
Sister chromatid exchange in vitro Chinese hamster ovary cells PMRA# 1155756	**Negative** up to 400 Φg/mL without activation and 1250 Φg/mL with activation
Sister chromatid exchange in vitro Chinese hamster ovary cells PMRA# 1155756	**Positive** at 500 µg/mL without activation (toxic dose) and 2000 µg/mL with activation

Study Type/ Animal/ PMRA#	Study Results
Mitotic recombination Saccharomyces cerevisiae strain D7 PMRA# 1155718	**Negative** for crossing-over in yeast up to 10,000 µg/mL with and without activation
DNA repair Bacillus subtilis strains H17 (Rec+) and H45 (Rec-) PMRA# 1155717	**Negative** up to 5000 µg/plate with and without activation
Unscheduled DNA synthesis in vitro Primary rat hepatocytes (♂ Fischer 344 rat) PMRA# 1155754	**Negative** up to 750 µg/mL, a toxic dose
GENOTOXICITY- Technical Imidacloprid (AMP-W process) containing two impurities i.e. N–[(6-chloro-3-pyridinyl)methyl] -1,2-ethanediamine (PEDA) and N, N'-bis-[6-chloro-3-pyridinyl) methyl] -1,2-ethanediamine (DIPEDA).	
Gene mutations in bacteria Salmonella typhimurium strains TA 98, TA 100, TA 1535 and TA 1537 PMRA# 1181354, 1181365	**Negative** up to 5000 :g/plate.
GENOTOXICITY – Desnitro-imidacloprid (metabolite)	
Reverse mutation assay Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537and E. coli strain WP2uvrA PMRA# 2030941	**Negative** up to 12500 :g/plate with activation and 2500 :g/ plate without activation.

Study Type/ Animal/ PMRA#	Study Results
GENOTOXICITY – Urea metabolite (mammalian metabolite)	
Reverse mutation assay Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 and E. coli strain WP2uvrA PMRA# 2030942	**Negative** up to 5000 :g/plate with and without activation
GENOTOXICITY – Olefin-imidacloprid (mammalian metabolite)	
Reverse mutation assay Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 and E. coli strain WP2uvrA PMRA# 2030943	**Negative** up to 5000 :g/ plate with and without activation.
GENOTOXICITY – Nitrosimine-imidacloprid (mammalian metabolite)	
Gene mutations in bacteria Salmonella typhimurium strains TA 98, TA 100, TA 1535 and TA 1537; E. Coli WP2uvrA PMRA# 1155715	**Negative** up to 5000 µg/plate with and without activation
Gene mutations in mammalian cells in vitro Chinese hamster V79 cells (HGPRT locus) PMRA# 1155707	**Negative** up to 2000 µg/mL with and without activation

Study Type/ Animal/ PMRA#	Study Results
Gene mutations in mammalian cells in vitro Chinese hamster ovary cells (HGPRT locus) PMRA# 1155702	**Negative** up to 2000 µg/mL with and without activation
Micronucleus assay (in vivo) BDF1 mouse (♂) Pilot study PMRA# 1155753	**Negative** up to 80 mg/kg bw. 2/5 died at 100 mg/kg bw in preliminary testing
Micronucleus assay (in vivo) BDF1 mouse (♂) Pilot study PMRA# 1155751	**Negative** up to 160 mg/kg bw. 1/5 died at 200 mg/kg bw in preliminary testing.
Micronucleus assay (in vivo) Bor:NMRI (SPF Han) mouse PMRA# 1155709	**Negative** up to 50 mg/kg bw. 100% lethality at 100 mg/kg bw in preliminary testing.
Micronucleus assay (in vivo) Bor:NMRI (SPF Han) mouse PMRA# 1155708	**Negative** up to 100 mg/kg bw. 1/10 died at 100 mg/kg bw in preliminary testing.
Chromosome aberrations in vitro Chinese hamster V79 cells PMRA# 1155703	**Negative** up to 1000 µg/mL with and without activation

Study Type/ Animal/ PMRA#	Study Results
Chromosome aberrations in vitro Chinese hamster ovary cells PMRA# 1155738	**Negative** up to 1000 µg/mL with and without activation
Unscheduled DNA synthesis in vitro Primary rat hepatocytes (♂) Wistar CF HB rats) PMRA# 1155713	**Negative** up to 1333 µg/mL
SPECIAL STUDIES	
Estrogen receptor binding assay Uterine cytosol from ovariectomized ♀ Sprague Dawley rat PMRA# 2182451	Negative for competitive binding with the estrogen receptor at 10^{-10} to 10^{-3} M.
Androgen receptor binding assay Prostate cytosol from castrated ♂ Sprague Dawley rat PMRA# 2182447	Negative for competitive binding with the androgen receptor at 10^{-10} to 10^{-3} M.
Estrogen receptor transcriptional activation assay Stably transfected hERα-HeLa-9903 cells (human cervical cancer cells) PMRA# 2182445	Negative for estrogen receptor transcriptional activation at 10^{-10} to 10^{-4} M.
Steroidogenesis assay H295R cells (human adrenocortical carcinoma cells) PMRA# 2182448	Negative for interference with steroidogenesis at 10^{-10} to 10^{-4} M. No inhibition or induction of testosterone or estradiol. Limitations in study conduct and reporting: no assessment of accuracy or precision of hormone measurement system was performed; cell viability detection method differed from guideline; cell viability data were not provided.

Study Type/ Animal/ PMRA#	Study Results
Aromatase assay Human recombinant aromatase (CYP 19) microsomes PMRA# 2182449	Negative for the inhibition of aromatase activity at 10^{-10} to 10^{-5} M.
Uterotrophic assay (gavage) Intact immature ♀ Sprague Dawley rat PMRA# 2182450	Negative for estrogenic activity. No effect on uterine wt. **100 mg/kg bw/day**: ↓ bw/bwg, piloerection with hunched posture. No assessment of anti-estrogenic effects
Hershberger assay (gavage) Castrated ♂ Sprague Dawley rat PMRA# 2182452	Negative for both androgenic and anti-androgenic activity. **80 mg/kg bw/day:** ↓ bw/bwg. No effect on the wts of five androgen-dependent tissues in castrated rats.
NON-GUIDELINE AND/OR SUPPLEMENTAL PUBLICATIONS	
Disposition and acute toxicity (gavage) Wistar rat (♀) PMRA# 2409253	Supplemental **20 mg/kg bw:** Salivation, diarrhea, piloerection and dyspnea at 6, 12, 24 and 48 hrs, tremors at 6 and 12 hrs, ↑ SGOT, SGPT, bilirubin, BUN, BChE, EChE. Peak concentrations of imidacloprid and metabolites 6-chloronicotinic acid (6-CNA) and 6-hydroxynicotinic acid (6-HNA) were seen at 12 hours in brain, blood, liver, kidney, ovary and urine. C_{max} for imidacloprid was in the order of urine > blood > brain > feces > liver > kidney > ovary. C_{max} for 6-CNA was urine > kidney > blood > feces > brain > liver > ovary. C_{max} for 6-HNA was urine > blood > feces > kidney > liver > ovary > brain (♀)
Acute in utero toxicity on GD9 (intraperitoneal) Sprague Dawley rat PMRA# 2418091	Supplemental **337 mg/kg bw(in utero):** PND 30 offspring demonstrated ↓ sensorimotor performance, ↑ AChE in cortex, ↑ ligand binding for muscarinic acetylcholine receptor (m2mAChR), ↑ GFAP immunostaining in sections of motor cortex and of hippocampus (no effect on ligand binding for nicotinic acetylcholine receptor α4β2nAChR); ↑ AChE in midbrain (♂); ↑ AChR in brainstem (♀)
Acute oxidant and inflammatory activity (intravenous) Wistar rat (♀) PMRA# 2417845	Supplemental **26 mg/kg bw:** 2 hours post-dose ↑ nitric oxide in brain, liver and plasma, ↑ MDA in liver and plasma, ↑ oxidant enzymes (xanthine oxidase and myeloperoxidase) in brain and liver, ↑ SOD in liver, ↑ glutathione peroxidase in brain, ↓ glutathione peroxidase in liver, ↓ glutathione in brain and liver, up-regulation of inflammatory markers TNF-α, IL-6 and IL-1β mRNA transcripts in brain and liver, down-regulation of anti-inflammatory cytokine IL-10 mRNA transcript in brain and liver, up-regulation of iNOS mRNA in liver, down-regulation of iNOS and nNOS mRNA in brain

Study Type/ Animal/ PMRA#	Study Results
Acute oral toxicity (gavage) Swiss albino mouse PMRA# 2417844	Supplemental **15 mg/kg bw:** ↑ MDA, ↓ GSH, ↑ CAT, ↑ SOD, ↑ GPx, ↑ GST in liver samples obtained 24h post dose. Co-treatment with 200 mg/kg bw vitamin C ameliorated all the above mentioned effects.
28 day oral toxicity study (gavage) Sprague Dawley rat(♂) PMRA# 2418125	Supplemental **80 mg/kg bw/day**:↓ total protein (Day 14/28), ↑ ALT, ↑ AST (Day 14/28), ↓ GSH, dilation and congestion of central hepatic vein (Day 14), moderate congestion, dilation of sinusoids and vacuolation of cytoplasm of hepatocytes/fatty change, severe congestion of the portal vein and degeneration of hepatocytes (Day 28), swollen hepatocyte nuclei, sinusoidal congestion, disrupted chromatin, varied size and shape of mitochondria and disrupted RER (Day 28) Co-treatment with 10 mg/kg bw vitamin C ameliorated the abovementioned effects.
60-day toxicity study (gavage) Wistar rat (♀) PMRA# 2409273	Supplemental; Confidor EP 17.2% **≥ 10 mg/kg bw/day:** diarrhea, ↓ PChE, ↓ BChE, mild inflammatory infiltration and moderate congestion of sinusoids of liver. (♀) **20 mg/kg bw/day:** ↑ salivation, sluggish movement, tremors, fatigue, ↓ fc, disturbed estrous cyclicity (↑ diestrous, ↓ estrous), ↓ relative heart and spleen wt, ↑ acid phosphatase, marked dilation and congestion of central vein and degeneration of hepatocytes. (♀)
13-week oral toxicity (gavage) Wistar rat (♀) PMRA# 2418109, 2418111	Non-guideline NOAEL for liver toxicity = 10 mg/kg bw/day **≥ 5 mg/kg bw/day:** ↓ BChE **10 mg/kg bw/day:** ↓ PChE activity, locomotor activity effects (↓ ambulatory time). **20 mg/kg bw/day:** clinical signs (diarrhea, salivation, dyspnea, piloerection), ↓ bw, ↓ fc, ↑ rel liver & kidney wts, ↑ biochemical parameters (SGOT,GPT, glucose, BUN), locomotor activity effects (↓ distance travelled, ↓ ambulatory time, ↓ stereotypic time, ↑ resting time), histopathological changes in the brain (necrosed Purkinje cells with loss of dendrites and granules in cerebellum), liver effects (mild focal necrosis with swollen cellular nuclei) and kidney effects (slight degeneration of tubules and glomeruli), ↓ rel ovary wt, ↑ FSH, ↓ LH, ↓ progesterone, ↑ lipid peroxidation in liver, kidney and ovary, oxidative stress assessments in liver, brain and ovary indicated ↓ catalase, ↓ SOD, ↓ glutathione, ↓ glutathione.
Micronucleus assay in vitro Human lymphocyte cells PMRA# 2418099	**Negative** up to 100 µg/mL without activation

Study Type/ Animal/ PMRA#	Study Results
Sister chromatid exchange in vitro Human lymphocyte cells PMRA# 2418099	**Negative** up to 100 µg/mL, without activation
Micronucleus assay in vivo Wistar rat PMRA# 2418099	**Negative** up to 200 mg/kg bw **Positive** at 300 mg/kg bw
nAChR toxicity Cerebellar cultures from neonatal rats PMRA# 2409279	Supplemental **1-100 µM:** intracellular excitatory Ca2+ influxes in cerebellar neurons which are mainly composed of granule cells. Calcium influx was inhibited by 3 nAChR antagonists suggesting imidacloprid has direct agonist activity at nAChR in cerebellar neurons; no effect on large-sized Purkinje cells on GFAP-positive astrocytes.
nAChR toxicity in stellate cells of mouse cochlear nucleus PMRA# 2418096	Supplemental **≥10 µM:** exposure for <1 minute changed membrane properties of the neurons tested. Co-exposure with nAChR antagonists d-tubocurarine or α-bungarotoxin blocked the reaction suggesting the involvement of nicotinic receptors
nAChR toxicity in mouse fibroblast M10 cells stably transfected with α4β2 AChR PMRA# 2418127, 2418129	Supplemental Cells exposed to imidacloprid, desnitro-imidacloprid or nicotine for 3 days showed ↑ [3H]-nicotine binding 5-8-fold (up-regulation of α4β2 AChR). Imidacloprid showed a low affinity and low potency to α4β2 AChR relative to nicotine but affinity and potency of desnitro-imidacloprid was comparable to nicotine. LD_{50}s in mice (i.p.) were 45, 8 and 0.08 mg/kg bw for imidacloprid, desnitro-imidacloprid and nicotine, respectively.
nAChR toxicity in mouse neuroblast N1E-115 cells stably transfected with α4β2 AChR PMRA# 2418131	Supplemental Desnitro-imidacloprid activates the extracellular signal-regulated kinase (ERK) cascade via interaction with neuronal α4β2 and intracellular Ca2+ in this cell population at 1 µM (similar to nicotine). Imidacloprid activation occurred at 100 µM.
nAChR binding in mouse brain Swiss Webster mouse PMRA# 2417850	Supplemental 50% inhibition of [3H]-nicotine binding with imidacloprid (12 nM), desnitro metabolite of imidacloprid (15 nM) and olefin—imidacloprid (83 nM). Corresponding intraperitoneal LD50s were 7-15, 16-24 and >50 mg/kg bw respectively. Nicotine binding 24-79-fold greater in housefly with imidacloprid and olefin-imidacloprid; nicotine binding greater in mouse than housefly with desnitro metabolite.
nAChE toxicity Human neuroblastoma cells, SH-SY5Y Torpedo electric organ PMRA# 2418127	Supplemental Alpha-containing nAChRs in Torpedo cells and α3- and α7- containing nAChR from human neuroblastoma cells were 2-4 fold more sensitive to desnitro-imidacloprid than to nicotine. Imidacloprid showed low affinity for the α1, α3 and α7 nAChR subtypes.

Study Type/ Animal/ PMRA#	Study Results
nAChE toxicity Human embryonic kidney (HEK 293) cell line stably expressing human α4β2 receptors PMRA# 2418114	Supplemental Weak activation of receptors with 300 µM imidacloprid compared to 1mM acetylcholine in patch-clamp assay. Imidacloprid acted as a competitive antagonist when co-applied with acetylcholine.
Case Reports of Intentional Imidacloprid Poisonings (Suicides) PMRA# 2417847, 2417846, 2417844, 2418123	Supplemental <u>Case 1: 69-year old female with possible pre-existing coronary arterial disease; 200 ml Confidor (9.6% a.i.)</u> Clinical signs included drowsiness, vomiting and diaphoresis 30 min after ingestion. Blood pressure was 170/73 mm Hg, temperature 35°C, respiration rate 24 breaths/min. Lesions in oropharynx. Tachycardia noted. Chest x-ray normal. Cardiac enzymes (including creatine kinase, creatine kinase MB isoform and troponin-I) considered normal. Cholinesterase inhibition tests were negative. Signs of severe cardiac toxicity including ventricular fibrillation were evident. Patient ultimately succumbed 12 hours after hospitalization to hypotension and arrhythmias. <u>Case 2:35-year old male; 350 ml imidacloprid(unknown purity)</u> Clinical signs included nausea, copious vomiting, disorientation, drowsiness, dizziness and heart palpitations 1 hour after ingestion. Pulse rate 130 bpm, blood pressure 165/95 mm Hg, mydriasis and apnea were evident. Hypokalemia, hypernatremia and elevated white blood cell count were observed. Cholinesterase activity was normal. Cardiopulmonary arrest occurred on the first day of admission and on day 6 of admission. Patient did not respond to advanced life support and died on day 6. <u>Case 3:67-year old male with possible pre-existing cardiovascular disease; Unknown volume; (18.2% a.i.)</u> Clinical signs included drowsiness and irritability. Blood pressure of 117/56 mm Hg, respiratory rate of 16 breaths/min. ECG was normal for sinus rhythm; left hypertrophy was indicated by voltage. Chest x-ray indicated cardiomegaly with right lower lung infiltration. Cardiac enzymes (including creatine kinase and troponin) were minimally increased while creatine kinase-MB was normal. Tachycardia, persistent high fever, anuria, and metabolic acidosis with partial compensation were observed. Cholinesterase inhibition test results were negative. 3 hours after admission, cyanosis, ventricular arrhythmia and cardiac arrest occurred. Patient was discharged against medical advice and died 3 days later. <u>Case 4:33-year old male, found dead. 66- year old male, found dead</u> At post-mortem, imidacloprid concentration in blood samples was 12.5 and 2.05 ug/ml and in liver samples was 9.9 and 1.01 ug/ml, respectively Additional observations noted in 66 year old male included chemical burns in the mouth and esophagous and pulmonary edema. Possible indications of chronic cardiac insufficiency.

Study Type/ Animal/ PMRA#	Study Results
Multiple case reports of Intentional Imidacloprid Poisonings (Suicides) PMRA# 2418115	Unspecified formulations containing 20% a.i. Mild symptoms noted in 54/56 cases included nausea, vomiting, headache, dizziness, abdominal pain and diarrhea; 2 required intensive medical management for respiratory failure or prolonged sedation. Exposure was confirmed in 28 with median admission plasma concentrations of 10.56 ng/L (range 0.02-51.25 ng/L). Median time to present to hospital was 4 hours post-ingestion. Median volume reported ingested was 15 mL (unknown in 23 cases). In 7 of the 8 cases with serial blood samples, imidacloprid remained elevated for 10-15 hrs post-ingestion.

Table 2 Toxicity Profile of Temprid SC Insecticide and Temprid ReadySpray Insecticide containing Imidacloprid

NOTE: Effects noted below are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons.

Study Type/ Animal/ PMRA #	Study Results
ACUTE STUDIES – Temprid SC Insecticide Insecticide (end-use product containing 21% imidacloprid and 10.5% beta-cyfluthrin)	
Oral (Up and Down Procedure) Sprague Dawley rat PMRA# 2073801	LD_{50} (♀) = 1044 mg/kg bw There were no clinical signs of toxicity or abnormal findings at necropsy. **SLIGHT TOXICITY**
Dermal Sprague Dawley rat PMRA# 2073804	LD_{50} (♂/♀) > 2000 mg/kg bw There were no clinical signs of toxicity or abnormal findings at necropsy. **LOW TOXICITY**
Inhalation (nose-only) Sprague Dawley rat PMRA# 2073807	LC_{50} (♂/♀) > 2.03 mg/L Following exposure all animals were hypoactive; however all animals recovered by Day 2. No abnormal findings at necropsy. **LOW TOXICITY**
Eye Irritation NZW rabbit PMRA# 2073808	MAS = 6 MIS = 21.3 at 1 hr **Minimally irritating**

Study Type/ Animal/ PMRA #	Study Results
Dermal Irritation NZW rabbit PMRA# 2073809	MAS = 1.33 MIS = 3.0 at 1 and 24 hrs **Slightly irritating**
Skin Sensitization- (Buehler) Hartley Guinea pig PMRA# 2073810	**Not a dermal sensitizer**
ACUTE STUDIES – Temprid ReadySpray Insecticide (end-use product containing 0.05% imidacloprid and 0.025% beta-cyfluthrin)	
Oral (Up and Down Procedure) Sprague Dawley rat PMRA# 2257258	LD_{50} (♀)>5000 mg/kg bw There were no clinical signs of toxicity or abnormal findings at necropsy **LOW TOXICITY**
Dermal Sprague Dawley rat PMRA# 2257259	LD_{50} (♂/♀) >5000 mg/kg bw There were no clinical signs of toxicity or abnormal findings at necropsy **LOW TOXICITY**
Inhalation	Bridged to Temprid SC Insecticide **LOW TOXICITY**
Eye Irritation NZW rabbit PMRA# 2257260	MAS = 0 MIS = 1.3 at 1 hr. **Non-irritating**
Dermal Irritation	Bridged to Temprid SC Insecticide **Slightly irritating**
Skin Sensitization	Bridged to Temprid SC Insecticide **Not a dermal sensitizer**

Table 3 Toxicology Endpoints for Use in Health Risk Assessment for Imidacloprid

Exposure Scenario	Dose (mg/kg bw/day)	Study	Endpoint	CAF or Target MOE[1]
Short-term dermal	NOAEL = 8	90-day dietary study in the dog	Clinical signs (trembling) during the first week of dosing and slight emaciation	100
Short-term inhalation	NOAEL = 8.4	28-day inhalation study in the rat	Liver, clinical chemistry and haematology changes	100
Non-dietary (incidental) oral (short-term)	NOAEL = 8	90-day dietary study in the dog	Clinical signs (trembling) during the first week of dosing and slight emaciation	100
Intermediate-term dermal and inhalation	NOAEL = 8	90-day dietary study in the dog	Clinical signs (trembling) during the first week of dosing and slight emaciation	100
Long-term dermal and inhalation	NOAEL = 5.7	2-year dietary study in the rat	An increased incidence of mineralized particles in the colloid of isolated follicles in the thyroid gland (males)	100
Aggregate short- and intermediate-term (all routes)	NOAEL = 8	90-day dietary study in the dog	Clinical signs (trembling) during the first week of dosing and slight emaciation	100
Aggregate long-term (all routes)	NOAEL = 5.7	2-year dietary study in the rat	An increased incidence of mineralized particles in the colloid of isolated follicles in the thyroid gland (males)	100
Acute dietary	NOAEL = 8	90-day dietary study in the dog	Clinical signs (trembling) during the first week of dosing and slight emaciation	100
	ARfD = 0.08 mg/kg bw			
Chronic Dietary	NOAEL = 5.7	2-year dietary study in the rat	An increased incidence of mineralized particles in the colloid of isolated follicles in the thyroid gland (males)	100
	ADI = 0.057 mg/kg bw/day			

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational and residential assessments.

Table 4 Pest Control Operator Dermal and Inhalation Exposure to Imidacloprid

Application Equipment	Amount Handled Per Day[1]	Unit Exposure (µg/ kg a.i. handled)[2]		Dermal Exposure (mg/kg bw/day)[3]	Dermal MOE [4]	Inhalation Exposure (mg/kg bw/day)[3]	Inhalation MOE[4]
		Dermal	Inhalation				
Temprid SC Insecticide							
Manually pressurized handwand	150 L /day	943.37	45.20	4.31×10^{-5}	132000	4.13×10^{-5}	138000
Backpack	150 L /day	5445.85	62.1	2.49×10^{-4}	22900	5.67×10^{-5}	100000
Temprid ReadySpray Insecticide							
Aerosol	14 cans per day	146598.1	1646	2.85×10^{-4}	20000	6.39×10^{-5}	89200

[1] Based on Agency default Amount Handled Per Day values and USEPA (2006).
[2] PHED single layer with chemical resistant gloves. Light inhalation except for backpack which is moderate.
[3] Exposure (mg/kg bw/day) = [(Amount Handled Per Day (L/day) × Dilution Rate (1.0 mL product/L) × Density for Temprid SC) **or** (Amount Handled Per Day (cans/day) × Net Contents (mL/can) × Density for Temprid ReadySpray)] × Guarantee (%) × Unit Exposure (µg/ kg a.i. handled) × Absorption Value (%) × Unit Conversion (mg/ 1000 µg)
[4] MOE = NOAEL (mg/kg bw/day) ÷ Exposure (mg/kg bw/day); Target MOE = 100

Table 5 Dermal Exposure to Imidacloprid from Treated Mattresses

Lifestage	Deposited Residue ($\mu g/cm^2$)	Surface area / Body weight Ratio (cm^2/kg)	Fraction of skin in contact with surface	Fraction transferred	Protection factor	Dermal Exposure (mg/kg/day)	Dermal MOE
Adults	2	280	0.5	0.06	0.5	0.00042	19000
Youth 11 < 16 years	0.97	280				0.000205	39100
Children 1 < 2 years		640				0.000468	17100

[1] For a full review of calculations, refer to USEPA Section 7 Indoor Environments SOP.

Table 6 Aggregate Exposure to Imidacloprid from Mattresses and the Diet

Lifestage	Dermal MOE [1]	Dietary MOE	Aggregate MOE [2]
Children (1 < 2 years)	17100	394	385

[1] Refer to Table 5

[2] The aggregate NOAEL is 8 mg/kg bw/day for dermal routes of exposure; NOEAL of 5.7 mg/kg bw/day for chronic dietary exposure; target MOE = 100
The aggregate MOE was calculated by, $= \frac{1}{[(1/MOE_{Dermal}) + (1/MOE_{Dietary})]}$

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

N/A

2.0 Human and Animal Health

PMRA Document Number	Reference
2073801	2007, Temprid SC (21% imidacloprid + 10.5% Beta-Cyfluthrin SC) Acute Oral Toxicity Up and Down Procedure in Rats, DACO: 4.6.1
2073804	2007, Temprid SC (21% imidacloprid + 10.5% Beta-Cyfluthrin SC) Acute Dermal Toxicity Study in Rats Limit Test, DACO: 4.6.2
2073807	2007, Temprid SC (21% imidacloprid + 10.5% Beta-Cyfluthrin SC) Acute Inhalation Toxicity Study in Rats - Limit Test, DACO: 4.6.3
2073808	2007, Temprid SC (21% imidacloprid + 10.5% Beta-Cyfluthrin SC) Primary Eye Irritation Study in Rabbits, DACO: 4.6.4
2073809	2007, Temprid SC (21% imidacloprid + 10.5% Beta-Cyfluthrin SC) Primary Skin Irritation Study in Rabbits, DACO: 4.6.5
2073810	2007, Temprid SC (21% imidacloprid + 10.5% Beta-Cyfluthrin SC) Dermal Sensitization Study in Guinea Pigs (Buehler Method), DACO: 4.6.6
2257258	2012, Temprid RTU Acute Oral Toxicity Up and Down Procedure in Rats, DACO: 4.6.1
2257259	2012, Temprid RTU Acute Dermal Toxicity Study in Rats, DACO: 4.6.2
2257260	2012, Temprid RTU Primary Eye Irritation Study in Rabbits, DACO: 4.6.4
2257261	2012, Bridging Rationale for the Acute Toxicology of Temprid RTU, DACO: 4.1,4.6.3,4.6.5,4.6.6
2257263	2012, Bridging Rationale for the Acute Toxicology of Temprid RTU, DACO: 4.1,4.6.3,4.6.5,4.6.6 CBI
591475	2001, A Developmental Neurotoxicity Screening Study with Technical Grade Imidacloprid in Wistar Rats, DACO: 4.5.12,4.5.14
1039613	1994, An Acute Oral Neurotoxicity Screening Study With Technical Grade Imidacloprid (NTN 33893) In Rats., DACO: 4.5.12
1039643	1994, A Subchronic Dietary Neurotoxicity Screening Study with Technical Grade Imidacloprid (NTN 33893) in Fischer 344 Rats., DACO: 4.5.13
1039650	1994, An Acute Oral Neurotoxicity Screening Study With Technical Grade Imidacloprid (NTN 33893) In Rats., DACO: 4.5.12
1039652	1994, A Subchronic Dietary Neurotoxicity Screening Study with Technical Grade Imidacloprid (NTN 33893) in Fischer 344 Rats., DACO: 4.5.13
1155681	NTN 33893 Technical: Subchronic Toxicity Study On Dogs In Oral Administration (Thirteen-Week Feeding Study) (100176;18732)(Imidacloprid/Admire), DACO: 4.3.1
1155682	NTN 33893: Subchronic Toxicity Study On Wistar Rats (Administration In The

	Feed For 96 Days)(100036;18187)(Imidacloprid/Admire), DACO: 4.3.1
1155687	NTN 33893 Technical: (Proposed C.N. Imidacloprid) Multiple Generation Reproduction Study In Rats (100647;R5097;RCC087063;T 7025163)(Admire), DACO: 4.5.1
1155688	NTN 33893 Technical: (Proposed C.N. Imidacloprid) Multiple Generation Reproduction Study In Rats (100647;R5097;RCC087063;T 7025163)(Admire), DACO: 4.5.1
1155689	NTN 33893 (Proposed Common Name: Imidacloprid) Subacute Inhalation Toxicity Study On The Rat According To OECD Guideline No.412 (100262;18199;T 3027635)(Admire), DACO: 4.3.6
1155690	NTN 33893 Technical: Study For Subacute Dermal Toxicity In The Rabbit (100688;19152)(Imidacloprid/Admire), DACO: 4.3.4
1155691	28-Day Oral Range-Finding Toxicity (Feeding) Study With Ntn 33893 Techn. In The Dog (99656;RCC 084993;T 6025018;R 4196)(Imidacloprid/Admire), DACO: 4.3.1
1155693	NTN 33893 Sister Chromatid Exchange In Bone Marrow Of Chinese Hamsters In Vivo Supplement Report To June 16 1989 REPORT (EPA MRID# 42256346)(99257-1;18093A;T8030302)(Imidacloprid/Admire), DACO: 4.5.4
1155694	Final Report Sister Chromatid Exchange Assay In Chinese Hamster Ovary Cells (99676;1149;T8302.334)(Imidacloprid/Admire), DACO: 4.5.4
1155695	WAK 3839 Subchronic Toxicological Study On Rats (Twelve-Week Administration In Drinking Water) (101949;21140;T 5033324)(Imidacloprid/Admire), DACO: 4.3.1
1155697	NTN 33893 Carcinogenicity Study On B6c3f1 Mice (Administration In The Food For 24 Months) (100693;19931)(Imidacloprid/Admire), DACO: 4.4.1,4.4.2
1155698	Embryotoxicity Study (Including Teratogenicity) With NTN 33893 Technical In The Rat Part I Revised Edition (98571;083496;148004;T 5032695)(Imidacloprid/Admire), DACO: 4.5.2
1155699	Embryotoxicity Study (Including Teratogenicity) With Ntn 33893 Technical In The Rabbit Part I Revised Edition (98572;083518)(Imidacloprid/Admire), DACO: 4.5.2
1155700	Mouse Germ-Cell Cytogenetic Assay With NTN 33893 (Imidacloprid/Admire) (102654;R 5063), DACO: 4.5.4
1155701	NTN 33893 In Vivo Cytogenetic Study Of The Bone Marrow In Chinese Hamster To Evaluate For Induced Clastogenic Effects (100021;18557;T 8032562)(Imidacloprid/Admire), DACO: 4.5.4
1155702	WAK 3839 Mutagenicity Study For The Detection Of Induced Forward Mutations In The Cho-Hgprt Assay In Vitro (17757;100661;T 7030167)(Imidacloprid/Admire), DACO: 4.5.4
1155703	Chromosome Aberration Assay In Chinese Hamster V79 Cells In Vitro With Wak 3839 (100666;R4849;CCR 151200)(Imidacloprid/Admire), DACO: 4.5.4
1155705	NTN 33893 Carcinogenicity Study In B6C3F1 Mice (Supplementary MTD Testing For Study T 5025710 With Administration In Diet Over A 24-Month Period)(101929;20769;T 4029986)(Imidacloprid/Admire), DACO: 4.4.1,4.4.2
1155706	NTN 33893 Mutagenicity Study For The Detection Of Induced Forward Mutations In The CHO-HGPRT Assay In Vitro (98587;17578;T 5029536)(Imidacloprid/Admire), DACO: 4.5.4
1155707	WAK 3839 Mutagenicity Study For The Detection Of Induced Forward Mutations

	In The V79-Hgprt Assay In Vitro (100662;18281)(Imidacloprid/Admire), DACO: 4.5.4
1155708	WAK 3839 Micronucleus Test On The Mouse After Oral Application (100663;184060(Imidacloprid/Admire), DACO: 4.5.4
1155709	WAK 3839 OR NTN 37571 Micronucleus Test On The Mouse After Intraperitoneal Injection (100664;18407)(Imidacloprid/Admire), DACO: 4.5.4
1155710	NTN 33893 Salmonella/Microsome Test To Evaluate For Point Mutagenic Effects (98570;17577;T 6030111)(Imidacloprid/Admire), DACO: 4.5.4
1155711	NTN 33893 In Vitro Cytogenetic Study With Human Lymphocytes For The Detection Of Induced Clastogenic Effects (99262;18092;T 6029654)(Imidacloprid/Admire), DACO: 4.5.4
1155713	Unscheduled Dna Synthesis In Primary Hepatocytes Of Male Rats In Vitro With WAK 3839 (100665;R4746;CCR 137002)(Imidacloprid/Admire), DACO: 4.5.4
1155714	NTN 33893 Reverse Mutation Assay (Salmonella Typhimurium And *Escherichia coli)* (101276;90A032)(Imidacloprid/Admire), DACO: 4.5.4
1155715	WAK 3839 Reverse Mutation Assay (*Salmonella typhimurium* and *Escherichia coli*) (100668;90A015;RA90035)(Imidacloprid/Admire), DACO: 4.5.4
1155717	NTN 33893 Rec-Assay With Spores In The Bacterial System (101275;90A013)(Imidacloprid/Admire), DACO: 4.5.4
1155718	NTN 33893 Test On S. Cerevisiae D7 To Evaluate For Induction Of Mitotic Recombination (102653;16832)(Imidacloprid/Admire), DACO: 4.5.4
1155720	NTN 33893 Study For Acute Inhalation Toxicity In The Rat In Accordance With OECD Guideline No. 403 (99806;16777)(Imidacloprid/Admire), DACO: 4.2.3
1155724	NTN 33893 Study For Acute Oral Toxicity To Rats (100040;18594)(Imidacloprid/Admire), DACO: 4.2.1
1155729	NTN 33893 (C.N. Imidacloprid (Proposed)) Study For Acute Dermal Toxicity To Rats (100041;18532)(Admire), DACO: 4.2.2
1155731	NTN 33893 Study For Irritant/Corrosive Potential On The Eye (Rabbit) According To OECD Guideline No. 405 (99679;16456;T 8025515)(Imidacloprid/Admire), DACO: 4.2.4
1155738	NTN 37571 In Vitro Cytogenetic Assay Measuring Chromosome Aberrations In CHO-K1 Cells (100678;RP880088)(Imidacloprid/Admire), DACO: 4.5.4
1155747	NTN 33893 Technical Study For Skin Sensitising Effect On Guinea Pigs (Maximization Test) (99800;16533;T 9025651)(Imidacloprid/Admire), DACO: 4.2.6
1155751	NTN 37571 Micronucleus Test On The Mice After Oral Treatment Pilot Study (100680;RS88040)(Imidaclorprid/Admire), DACO: 4.5.4
1155753	NTN 37571 Micronucleus Test On The Mice After I.P. Treatment Pilot Study (100679;RS88041)(Imidacloprid/Admire), DACO: 4.5.4
1155754	Mutagenicity Test On NTN 33893 In The Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay (98573;HLA 10237-0-447;T6027610;4631) Final Report (Imidacloprid/Admire), DACO: 4.5.4

1155755	NTN 33893 Micronucleus Test On The Mouse To Evaluate For Clastogenic Effects (102652;16837)(Imidacloprid/Admire), DACO: 4.5.4
1155757	NTN 33893 (Proposed Common Name: Imidacloprid) Chronic Toxicity And Carcinogencity Studies On Wistar Rats (Administration In Food Over 24 Months) Supplementary MTD Study For Two-Year Study T 1025699 (101931;20541;T3030055;T 1025699)(Admire), DACO: 4.4.
1155758	52-Week Oral Toxicity (Feeding) Study With NTN 33893 TECHNICAL IN THE DOG (085004;T 7025019;R 4856;100015)(Imidacloprid/Admire), DACO: 4.4.1
1155760	NTN 33893 (Proposed Common Name: Imidacloprid) Chronic Toxicity And Cancerogenicity Studies On Wistar Rats (Administration In Food Over 24 Months) (100652;19925)(Admire)(Cont'd On Roll# 1315), DACO: 4.4.1
1155761	(Cont'd From Roll#1314) NTN 33893 (Proposed Common Name: Imidacloprid) Chronic Toxicity And Cancerogenicity Studies On Wistar Rats (Administration In Food Over 24 Months) (100652;19925)(Admire), DACO: 4.4.1,4.4.2
1155769	Methylene- [14-C] Imidacloprid: Metabolism Part Of The General Metabolism Study In The Rat (101999;M 182 0176-5)(ADMIRE), DACO: 4.5.9,6.4
1155781	Imidacloprid- WAK 3839: Comparison Of Biokinetic Behaviour And Metabolism In The Rat Following Single Oral Dosage And Investigation Of The Metabolism After Chronic Feeding Of Imidacloprid To Rats And Mice (100645;PF 3432;M 71810016)(Admire), DACO: 4.5.9
1155782	[Imidazolidine-4,5-14c] Imidacloprid: Investigation Of The Biokinetic Behaviour And Metabolism In The Rat (102617;PF 3629;M 31819004)(Admire), DACO: 4.5.9,6.4
2030936	1993, NTN 38014 - Acute oral toxicity study on rats, DACO: 4.2.1
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2030938	1993, NTN 35884 - Acute oral toxicity study on rats, DACO: 4.2.1
2030939	1991, NTN 33893 AMP (proposed c.n.: Imidacloprid) - Study for acute oral toxicity to rats, DACO: 4.2.1
2030940	1991, NTN 33893 CNS (c.n.: Imidacloprid (proposed) - Study for acute oral toxicity in rats, DACO: 4.2.1
2030941	1991, NTN 38014 - Reverse mutation assay (Salmonella typhimurium and Escherichia coli), DACO: 4.5.4
2030942	1991, NTN 33519 - Reverse mutation assay (Salmonella typhimurium and Eschericha coli), DACO: 4.5.4
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2030947	1987, (14C)-NTN 33893: Biokinetic part of the 'General metabolism study' in the rat, DACO: 4.5.9
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2182451	2012, Evaluation Of Imidacloprid In The Estrogen Receptor Binding Assay, DACO: 4.8
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PMRA Document Number	Reference
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3.0 Environment

N/A

4.0 Value

PMRA Document Number	Reference
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2073785	2010, Temprid SC Insecticide (21% Imidacloprid, 10.5% Beta-cyfluthrin) For Control Public Health Pests (Such As Bed Bugs) And Certain General Indoor Household Pests And Outdoor Pests, DACO: 10.1,10.2.1,10.2.2,10.2.3.1,10.2.3.3,10.3.1,10.3.2
2073787	Temprid spreadsheet 2010 Data Summary Excel tables Feb19, DACO: 10.2.3.3
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2310242	Temprid SC Insecticide (Sub. No. 2011-2689): Response to Request for Clarification. DACO 0.8
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B. Additional Information Considered

i) Published Information

1.0 Chemistry

na

2.0 Human and Animal Health

PMRA Document Number	Reference
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2418098	Brunet, Jean-Luc et al, 2003, Human intestinal absorption of imidacloprid with Caco-2 cells as enterocyte model - Toxicology and Applied Pharmacology, Volume 194, Pages 1 to 9, DACO: 4.8
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2418125	Soujanya, S. et al, 2013, Evaluation of the protective role of vitamin C in imidacloprid¿¿¿induced hepatotoxicity in male Albino rats - Journal of Natural Science, Volume 4, Issue 1, Pages 63 to 67, DACO: 4.8
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N/A	2012, USEPA. Standard Operating Procedures for Residential Pesticide Exposure Assessment: Section 7 Indoor Environments. Health Effects Division, Office of Pesticide Programs, Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency, Washington, DC

3.0 Environment

N/A

4.0 Value

N/A

ii) Unpublished Information

1.0 Chemistry

N/A

2.0 Human and Animal Health

N/A

3.0 Environment

N/A

4.0 Value

N/A